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(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : WITZEL, Bruce, E. [US/US]; 115 Scotch Plains Avenue, Westfield, NJ 07090 (US). TOLMAN, Richard, L. [US/US]; 29 Upper Warren Way, Warren, NJ 07059 (US).

(74) Agent: GRASSLER, Frank, P.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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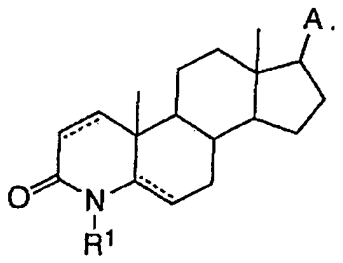
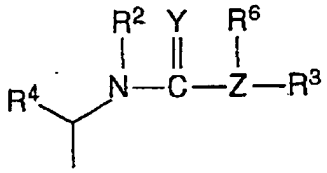
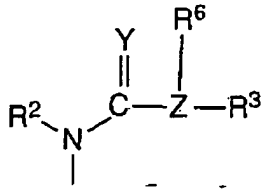
(54) Title: 4-AZASTEROID 5-ALPHA-REDUCTASE INHIBITORS



(I)



(a)



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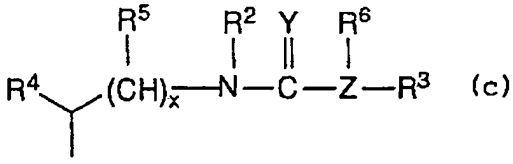

(c)

(57) Abstract

Novel substituted 4-azasteroid 5-α-reductase inhibitors of formula (I), wherein A is (a), (b) or (c), are claimed as well as pharmaceutically acceptable salts and formulations thereof. These compounds are effective inhibitors of testosterone 5α-reductase(s) and are thus useful in the treatment of a number of hyperandrogenic conditions including benign prostatic hypertrophy, acne, seborrhea, female hirsutism, and male and female pattern baldness (alopecia).

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TITLE OF THE INVENTION

4-AZASTEROID 5-ALPHA-REDUCTASE INHIBITORS

BACKGROUND OF THE INVENTION

The present invention is directed to novel urea, thiourea, thiocarbamyl and carbamyl 4-azasteroidal 5-alpha-reductase inhibitors.

The art reveals that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, male pattern baldness and benign prostatic hypertrophy, are the result of hyperandrogenic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system. Early attempts to provide a chemotherapeutic agent to counter the undesirable results of hyperandrogenicity resulted in the discovery of several steroidal antiandrogens having undesirable hormonal activities of their own. The estrogens, for example, not only counteract the effect of the androgens but have a feminizing effect as well. Non-steroidal antiandrogens have also been developed, for example, 4'-nitro-3'-trifluoromethyl- isobutyranilide. See Neri, et al., Endo., Vol. 91, No. 2 (1972). However, these products, though devoid of hormonal effects, are peripherally active, competing with the natural androgens for receptor sites, and hence have a tendency to feminize a male host or the male fetus of a female host

It is now known in the art that the principal mediator of androgenic activity in some target organs is 5α-dihydrotestosterone, and that it is formed locally in the target organ by the action of testosterone-5α-reductase. It is also known that inhibitors of testosterone-5α-reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation. A number of 4-aza steroid compounds are known in the art that are 5α-reductase inhibitors. For example, see U.S. Patent Nos. 2,227,876, 3,239,417, 3,264,301 and 3,285,918; French Patent No. 1,465,544; Doorenbos and Solomons, J. Pharm. Sci. 62, 4, pp. 638-640 (1973); Doorenbos and Brown, J. Pharm. Sci., 60, 8, pp. 1234-1235

(1971); and Doorenbos and Kim, J. Pharm. Sci. 63, 4, pp. 620-622 (1974).

In addition, U.S. Patent Nos. 4,377,584, 4,220,775, 4,859,681, 4,760,071 and the articles J. Med. Chem. 27, p. 1690-1701 (1984) and J. Med. Chem. 29, 2998-2315 (1986) of Rasmusson, et al., U.S. Patent 4,845,104 to Carlin, et al., and U.S. Patent 4,732,897 to Cainelli, et al. describe 4-aza-17ß-substituted-5α-androstan-3-ones which are said to be useful in the treatment of DHT-related hyperandrogenic conditions.

However, despite the suggestion in the prior art that hyperandrogenic diseases are the result of a single 5α-reductase, there are reports regarding the presence of other 5α-reductase isozymes in both rats and humans. For example, in human prostate, Bruchovsky, et al. (See J. Clin. Endocrinol. Metab. 67, 806-816, 1988) and Hudson (see J. Steroid Biochem. 26, p 349-353, 1987) found different 5α-reductase activities in the stromal and epithelial fractions. Additionally, Moore and Wilson described two distinct human reductases with peaks of activities at either pH 5.5 or pH 7-9. (See J. Biol. Chem. 251, 19, p. 5895-5900, 1976.)

Recently, Andersson and Russell isolated a cDNA which encodes a rat liver 5α-reductase (see J. Biol. Chem. 264 pp. 16249-55 (1989). They found a single mRNA which encodes both the liver and prostatic reductases of rats. A sequence of this rat gene was later used to select a human prostatic cDNA encoding a 5α-reductase termed "5α-reductase 1". (See Proc. Nat'l. Acad. Sci. 87, p. 3640-3644, 1990.)

More recently, a second, more abundant reductase (5α-reductase 2) has been cloned from human prostate with properties identified with the form found in crude human prostatic extracts. (See Nature, 354, p. 159-161, 1991.)

Further, "Syndromes of Androgen Resistance" - The Biology of Reproduction, Vol. 46, p. 168-173 (1992) by Jean O. Wilson indicates that the 5α-reductase 1 enzyme is associated with hair follicles.

Thus, the art supports the existence of at least two genes for 5α-reductase and two distinct isozymes of 5α-reductase in humans.

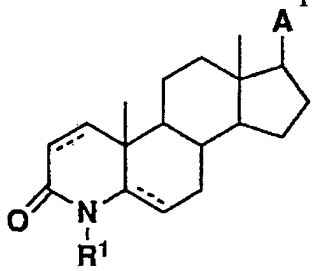
Both forms are present in prostatic tissue in which, 5α-reductase 2, is the more abundant, and the other isozyme, 5α-reductase 1, is believed to be more abundant in scalp tissue.

In the treatment of hyperandrogenic disease conditions, e.g. benign prostatic hyperplasia (BPH) it would be desirable to have one drug entity which is active against both enzymes 1 and 2 in the prostate to substantially inhibit dihydrotesterone (DHT) production. Alternatively, it would be desirable to have a drug entity which is highly selective for inhibiting the scalp associated enzyme 5α-reductase 1, for use in treating diseases of the skin and scalp, e.g. acne and alopecia. This latter drug could be used in combination with PROSCAR® (finasteride) which is highly selective for the prostatic enzyme 5α-reductase 2 for combination therapy in the treatment of BPH.

SUMMARY OF THE INVENTION

The present invention is concerned with novel 4-azasteriodal ureas, thioureas, thiocarbamates and carbamates and pharmaceutical compositions and formulations thereof that are useful for inhibiting the 5α-reductase isozymes 1 and 2 and are particularly effective in selectively inhibiting the 5α-reductase 1 associated with the scalp and dually inhibiting both isozymes 1 and 2 in the oral, parental or topical treatment of benign prostatic hyperplasia, acne, female hirsutism, male pattern baldness, androgenic alopecia, prostatitis, and the prevention and treatment of prostatic carcinoma.

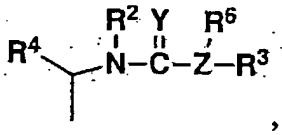
The present invention claims compounds of the formula:

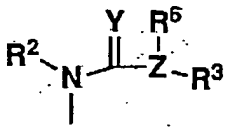


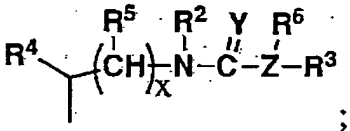
I

and the pharmaceutically acceptable salts thereof, wherein:

A is:

(a)  ,

(b)  except when R^2 equals H, Y equals O, Z equals N and there is a 5αH, R^6 and R^3 cannot be independently selected from H, C_{1-8} alkyl, C_{3-6} cycloalkyl, phenyl or when R^6 and R^3 are taken together with the adjacent N to form a 5-6 membered ring comprising up to one other heteroatom selected from O or N, or

(c)  ; wherein

R^1 is:

H, methyl or ethyl;

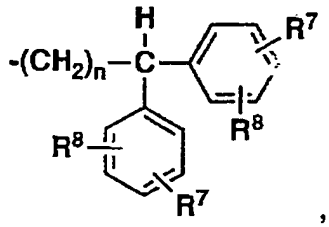
R^2 is:

H, or
C_{1-20} alkyl;

R^3 is:

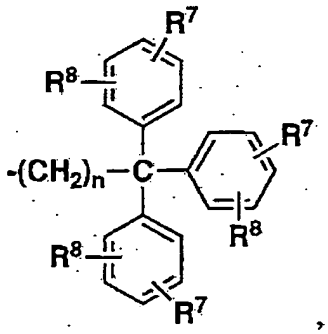
H,
amino,
mono C_1-C_4alkylamino,
di C_1-C_4alkylamino,

mono C1-C4 alkylaminoaryl,
di C1-C4 alkylaminoaryl,
C1-20 alkyl,
C6-14 aryl,
heteroaryl,
C6-14 arylC1-20alkyl,
C3-20cycloalkyl,
C3-20cycloalkylC1-20alkyl,
heteroarylC1-20alkyl,
C2-20 alkenylC1-20alkyl,
haloC1-20alkyl,
C1-20alkyloxycarbonylC1-20alkyl,
C1-20alkyloxyC1-20alkyl,
carboxylC1-20alkyl,
C6-14 arylcarbonylC6-14arylC1-20alkyl,
C1-20alkylcarbonylC1-20alkyl,
C6-14 arylC1-20alkyloxycarbonylC1-20alkyl,
heteroarylC1-20alkyloxycarbonylC1-20alkyl,
hydroxylC1-20alkyl,
halohydroxylC1-20alkyl,
C6-14 arylC1-20alkyloxyC1-20alkyl,
heteroarylC1-20alkyloxyC1-20alkyl,
carboxylC1-20alkyl,
C1-20alkylcarbonylC1-20alkyl,
thiosulfatoC1-20alkyl,
diarylC1-20alkyl of the formula:



, n equals 0-19;

triarylC1-20alkyl of the formula:



, n equals 1-19;

C_{2-20} alkenyl,
C_{2-20} alkenylC_{1-20}alkyl,
C_{2-20}alkynylC_{1-20}alkyl,
C_{6-14} arylC_{2-20}alkynylC_{1-20}alkyl,
heteroarylC_{2-20}alkynylC_{1-20}alkyl,
C_{1-20}alkylthioC_{1-20}alkyl,
C_{1-20}alkylsulfonylC_{1-20}alkyl, or
C_{1-20}alkylsulfinylC_{1-20}alkyl;

R^4 is:

H,
C_{1-20} alkyl,
C_6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen; or
heteroaryl;

R^5 can be the same or different when x is greater than 1 and is:
H, or

C_{1-12} alkyl,
heteroaryl, or
C_{6-14} aryl;

R^6 is present when Z equals N and is independently
H,
C_{1-20} alkyl, or
equivalent to R^3; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

R^7 or R^8 are:

H,
CH_3,
C_2H_5,
carboxamido,
OH,
OCH_3,
NO_2,
CN,
F,
RS,
RSO,
RSO_2,
R_2N, where R can be the same or different selected from H, C_1-C_4 alkyl, or C_6-C_{10} aryl;
Cl,
acetamido,
OC_2H_5,
CF_3,
isopropyl, or
isobutyl; n equals 1-10 and the C_{1-20}alkyl portion is optionally substituted with R^5;

Y is:

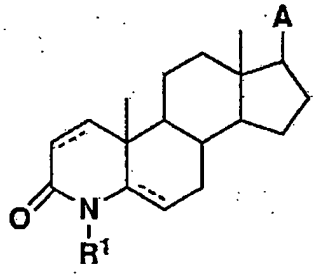
O, or
S;

Z is:

N, or
O;

x is an integer from 1-25 and dashes indicate a double bond is optionally present.

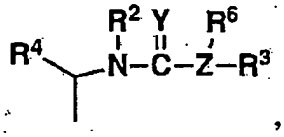
Advantageously, compounds of the following formula are disclosed in the present invention.

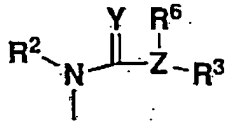


I

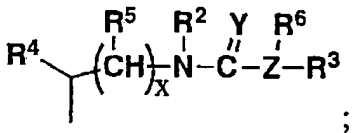
and the pharmaceutically acceptable salts thereof, wherein:

A is:

(a)  ,

(b)  except when R^2 equals H, Y equals O, Z equals N and there is a 5αH, R^6 and R^3 cannot be independently

selected from H, C_{1-8} alkyl, C_{3-6} cycloalkyl, phenyl or when R^6 and R^3 are taken together with the adjacent N to form a 5-6 membered ring comprising up to one other heteroatom selected from O or N, or

(c)  ; wherein

R^1 is:

H, methyl or ethyl;

R^2 is:

H, or
C_{1-20} alkyl;

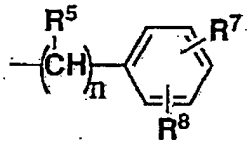
R^3 is:

H,
C_{1-20}alkyl is a straight or branched chain alkane of up to 20 carbon atoms;

C_{6-14} aryl wherein aryl is a mono or polycyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamido or halogen;

heteroaryl which is a mono or polycyclic system composed of 5- or 6-membered aromatic rings consisting of 1,2, 3 or 4 heteroatoms chosen from N, O, or S and either unsubstituted or substituted with R or independently with hydroxyl, C_{1-20}alkyloxy, C_{1-20}alkyl, benzoyl, carboamide, acetamide, halogens, C_{2-20}alkenyl, cyano, nitro, or haloalkyl directly bonded to the aromatic carbon atoms(s);

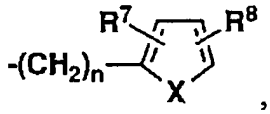
C_{6-14} arylC_{1-20}alkyl of the formula:



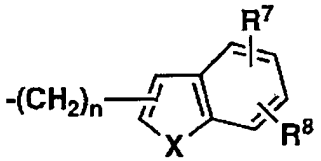
wherein the aromatic ring is optionally and independently substituted with R^7 and R^8 wherein R^7 and R^8 are
H,
CH_3,
C_2H_5,
carboxamido,
OH,
OCH_3,
NO_2,
CN,
F,
RS,
RSO,
RSO_2,
R_2N, where R can be the same or different selected from H, C_1-C_4 alkyl, or C_6-C_{10} aryl;
Cl,
acetamido,
OC_2H_5,
CF_3,

isopropyl, or
isobutyl; n equals 1-10 and the C_{1-20}alkyl portion is optionally substituted with R^5;

HeteroarylC$_{1-20}$alkyl of the formula:



, or

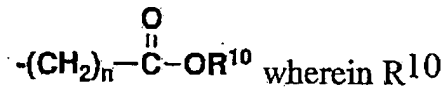


wherein X equals O, S, or NR; and n equals 1-20;

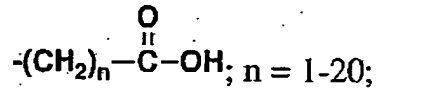
C$_{1-20}$alkylsulfonylC$_{1-20}$alkyl,
C$_{1-20}$alkylthioC$_{1-20}$alkyl,
C$_{1-20}$alkylsulfinylC$_{1-20}$alkyl of the formula:

$-(CH_2)_nS(O)_p-R^9$ wherein R^9 is
CH_3,
C_2H_5,
C_3H_7,
C_4H_9,
isopropyl,
isobutyl,
sec-butyl,
t-butyl,
isopentyl,
neopentyl, or
ixohexyl; n equals 1-15 and p=0-2;

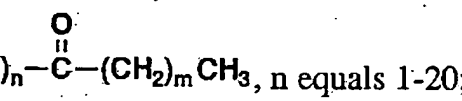
C$_{1-20}$alkyloxycarbonylC$_{1-20}$alkyl of the formula:


wherein R^{10} is:
CH_3,
C_2H_5,
C_3H_7,
C_4H_9, or
C_5H_{11}; and n equals 1-20;

CarboxylC_{1-20}alkyl of the formula:

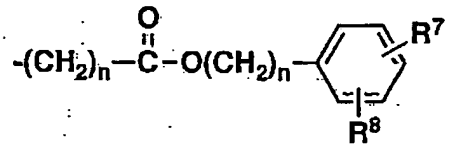

; n = 1-20;

C_{1-20}alkylcarbonylC_{1-20}alkyl of the formula


, n equals 1-20;
m equals 0-19;

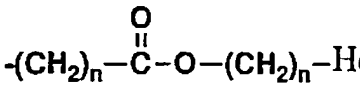
C_{3-20}cycloalkylC_{1-20}alkyl of the formula:
$-(CH_2)_n$-(cycloalkyl) wherein the cycloalkyl protion is a monocyclic, bicyclic, or polycyclic hydrocarbon of up to 20 carbon atoms wherein the rings are optionally substituted with R^1; and n = 1-20;

ArylC_{1-20}alkyloxycarbonylC_{1-20}alkyl of the formula:



wherein R^7 and R^8 are as defined; n equals 1-20;

HeteroarylC1-20alkyloxycarbonylC1-20alkyl of the formula:



wherein Heteroaryl is as defined and n = 1-20;

haloC1-20 alkyl of the formula:

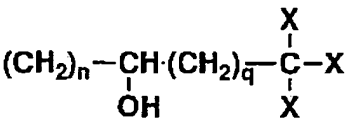
$-(CH_2)_n-CH_2X$ wherein

X equals Br, Cl, F or I; n is 1-19;

hydroxylC1-20alkyl of the formula:

$-(CH_2)_nCH_2OH$; n is 1-19;

halohydroxylC1-20alkyl of the formula:



wherein

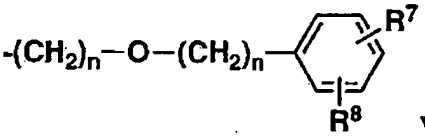
n = 1-18

q = 0-18

n + q = 0-18 and

X equals Br, Cl, F or I;

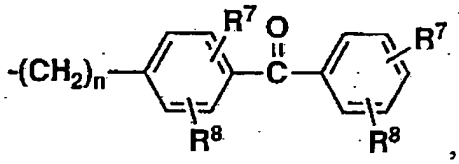
C6-14ArylC1-20alkyloxyC1-20alkyl of the formula:



wherein

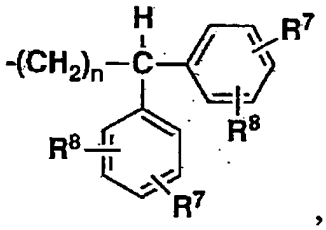
R^7 and R^8 are as defined; n is 1-20;

ArylcarbonylarylC1-20alkyl of the formula:



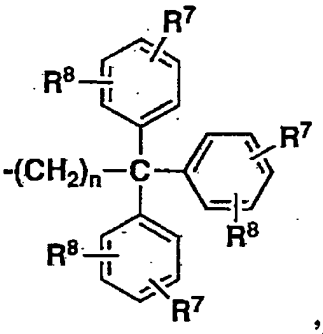
, n equals 1-20;

DiarylC1-20alkyl of the formula:



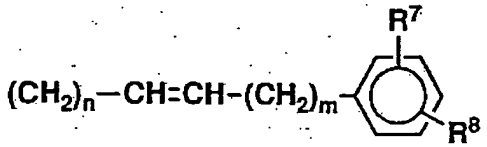
, n equals 0-19;

TriarylC1-20alkyl of the formula:



, n equals 1-19;

Aryl C2-20alkenyl of the formula:



n = 0-18
m = 0-18
m+n = 0-18;

R^4 is

H,
C_{1-20}alkyl,
C_6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen; or

heteroaryl;

R^5 can be the same or different when x is greater than one and is;
H, or
C_{1-12}alkyl;

R^6 is present when Z equals N and is independently
H,
C_{1-20} alkyl, or
equivalent to R^3; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

Y is:

O, or
S;

Z is:

N, or
O;

x is an integer from 1-10 and dashes indicate a double bond is optionally present.

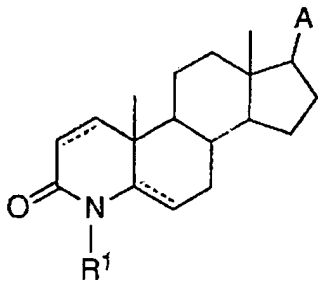
The present invention is particularly concerned with providing a method of treating the hyperandrogenic conditions of androgenic alopecia, acne vulgaris, seborrhea, and female hirsutism by topical and/or oral administration, and a method of treating all of the above conditions as well as benign prostatic hyperplasia, prostatitis, the prevention and/or treatment of prostatic carcinoma, by oral or parenteral administration, of the novel compounds of the present invention.

The present invention is thus also concerned with providing suitable topical, oral and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION:

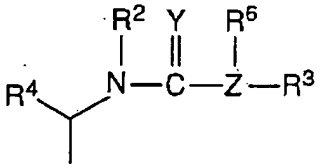
The present invention is concerned with novel 4-azasteroidal ureas, thioureas, and carbamates and pharmaceutical compositions and formulations thereof that are useful as testosterone 5α-reductase inhibitors to treat various hyperandrongenic conditions including acne vulgaris, seborrhea, female hitsutism, male and female pattern baldness, benign prostatic hypertrophy, prostatitis, androgenic alopecia, and the prevention and treatment of prostatic carcinoma. Advantageously, the compounds of the invention may be used to treat scalp disorders by selectively inhibiting 5α-reductase 1 or the compounds may be used as dual inhibitors of 5α-reductase 1 and 2 to treat the above disorders.

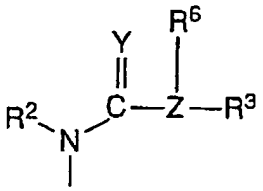
The present invention is concerned with compounds of the formula:



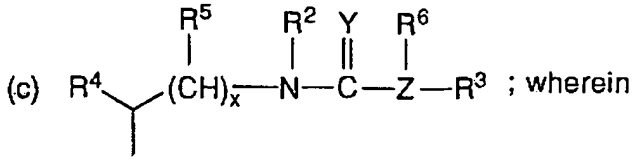
and the pharmaceutically acceptable salts thereof, where:

A is:

(a) 

(b) 

except when R^2 equals H, Y equals O, Z equals N, and there is a 5α H, R^6 and R^3 may not be independently selected from H, C_{1-8} alkyl, C_{3-6} cycloalkyl, phenyl or when R^6 and R^3 are taken together with the adjacent N to form a 5-6 membered ring comprising up to one other heteroatom selected from O or N, or

(c)  ; wherein

R^1 is:

H,
C_{1-20}alkyl;

R^2 is:

H, or methyl or ethyl;

R^3 is:

H,
C_{1-20} alkyl,
C_{5-14} aryl,
heteroaryl,
C_{5-14} arylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{3-20} cycloalkyl,
C_{3-20} cycloalkylC_{1-20}alkyl,
C_{2-20} alkenylC_{1-20}alkyl,
haloC_{1-20}alkyl,
C_{1-20} alkyloxyC_{1-20}alkyl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
C_{1-20} alkylthioC_{1-20}alkyl,
C_{1-20} alkylsulfonylC_{1-20}alkyl,
C_{1-20}alkylsulfinylC_{1-20}alkyl,
carboxyC_{1-20} alkyl,
C_{6-14} arylcarbonylarylC_{1-20}alkyl
C_{1-20} alkylcarbonylC_{1-20}alkyl,
C_{6-14} arylC_{1-20} alkyloxycarbonylC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
haloC_{1-20}alkyl,
hydroxyC_{1-20}alkyl,
halohydroxylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxyC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxyC_{1-20}alkyl,
diarylC_{1-20}alkyl,

triarylC_{1-20}alkyl,
C_{2-20} alkenyl,
C_{2-20} alkenylC_{1-20}alkyl,
C_{2-20} alkynylC_{1-20}alkyl,
C_{6-14} arylC_{2-20}alkynylC_{1-20}alkyl, or
heteroarylC_{2-20}alkynylC_{1-20}alkyl;

R^4 is:

H,
C_{1-20} alkyl,
heteroaryl, or
C_{6-14} aryl;

R^5 can be the same or different when x is greater than 1 and is:

H,
C_{1-20} alkyl,
heteroaryl, or
C_{6-14} aryl;

R^6 is present when Z equals N and is

H, or
C_{1-20} alkyl; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

Y is:

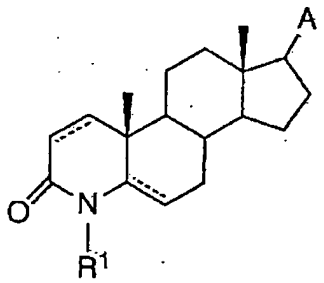
O, or
S;

Z is:

N, or
O;

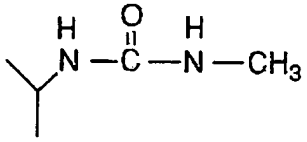
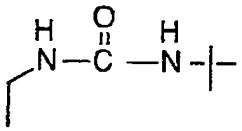
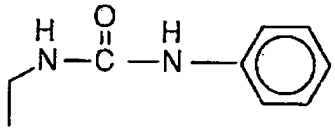
x is an integer from 1-25, and dashes indicate a double bond is optionally present.

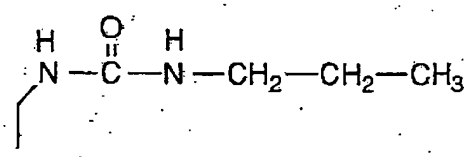
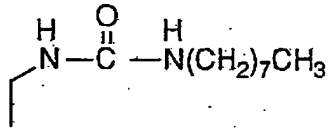
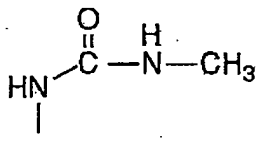
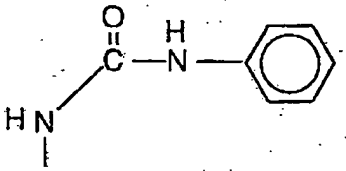
Compounds of the formula:

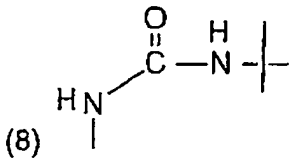


are representative of the compounds claimed in the instant invention. In a preferred embodiment, R^1 may be H or CH_3 and A may be as indicated as in Table 1. Particular representative chemical names are also listed in Table 1 adjacent to the respective side chain and specifically reflect whether the 1-position is saturated or unsaturated. Advantageously, R^1 is CH_3, A is as indicated in Table 1 and the 1 position is saturated. Unless otherwise indicated, the 17-position substituent is assumed to be on the beta configuration.

TABLE 1

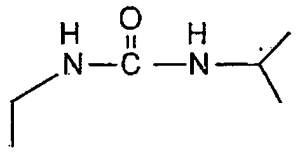
	Side Chain A	Compounds
(1)		4-Methyl-20-(N'-methyl-ureido)-5α-4-azapregn-1-en-3-one
		4-Methyl-20-(N'-methyl-ureido)-5α-4-azapregnan-3-one
(2)		17-(N'-t-butylureido-methyl)-4-methyl-5α-4-aza-androst-1-en-3-one
		17-(N'-t-butylureido-methyl)-4-methyl-5α-4-aza-androstan-3-one
(3)		4-Methyl-17-(N'-phenyl-ureidomethyl)-5α-4-aza-androst-1-en-3-one
		4-Methyl-17-(N'-phenyl-ureidomethyl)-5α-4-aza-androstan-3-one

Side Chain (A)	Compound(s)
(4) 	4-Methyl-17-(N'-n-propyl-ureidomethyl)-5α-4-aza androst-1-en-3-one 4-Methyl-17-(N'-n-propyl-ureidomethyl)-5α-4-aza-androstan-3-one
(5) 	4-Methyl-17-(N'-n-octyl-ureidomethyl)-5α-4-aza-androstan-3-one 4-Methyl-17-(N'-n-octyl-ureidomethyl)-5α-4-aza-androstan-3-one
(6) 	4-Methyl-17-(N'-methyl-ureido)-5α-4-azaandrost-1-3n-3-one 4-Methyl-17-(N'-methyl-ureido)-5α-4-azaandrost-1-an-one
(7) 	4-Methyl-17-(N'-phenyl-ureido)-5α-4-azaandrost-1-en -3-one 4-Methyl-17-(N'-phenyl-ureido)-5α-4-azaandrost-an-3-one

(8) 

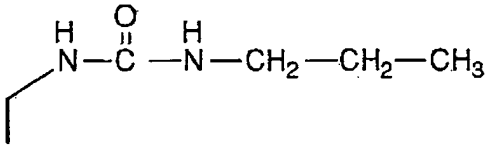
17-(N'-t-butylureido)4-methyl-5α-4-azaandrost-1-en-3-one

17-(N'-t-butylureido)4-methyl-5α-4-azaandrostan-en-3-one

(9) 

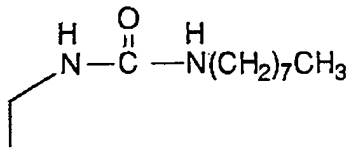
17-(N'-isopropylureido-methyl)4-methyl-5α-4-azaandrost-1-en-3-one

17-(N'-isopropylureido-methyl)4-methyl-5α-4-azaandrostan-3-one

(10) 

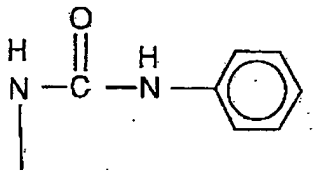
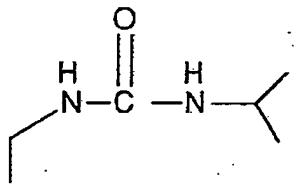
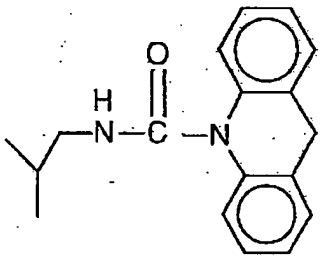
4-Methyl-17β(N'-n-propyl-ureidomethyl)5α-4-aza-androstan-3-one

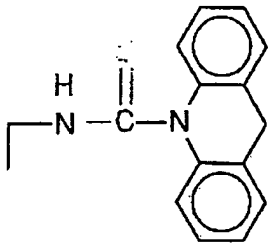
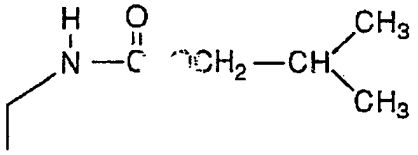
4-Methyl-17β(N'-n-propyl-ureidomethyl)5α-4-azaan-drost-1-en-3-one

(11) 

4-Methyl-17β-(N'-n-octyl-ureidomethyl)5α-4-azaan-drost-1-en-3-one

4-Methyl-17β-(N'-n-octyl-ureidomethyl)5α-4-azaan-drostan-3-one

Side Chain (A)	Compounds
(12) 	4-Methyl-17β-(N'-phenyl-ureido)-5α-4-azaandrost-an-3-one
	4-Methyl-17β-(N'-phenyl-ureido)-5α-4-azaandrost-1-en-3-one
(13) 	17β-(N'-Isopropylureido-methyl)-4-methyl-5α-4-azaandrostan-3-one
	17β-(N'-Isopropylureido-methyl)-4-methyl-5α-4-azaandrostan-3-one
(14) 	20-((Iminodibenz-5-yl)-carbonylaminomethyl)-4-methyl-5α-4-aza-pregan-3-one
	20-((Iminodibenz-5-yl)-carbonylaminomethyl)-4-methyl-5α-4-aza-pregan-1-en-3-one

	Side Chain (A)	Compounds
(15)		17β-((Iminodibenz-5-yl)-carbonylaminomethyl)-4-methyl-5α-4-aza-androstan-3-one 17β-((Iminodibenz-5-yl)-carbonylaminomethyl)-4-methyl-5α-4-aza-androstan-3-one
(16)		17β-(Isobutyloxycarbonyl-aminomethyl)-4-methyl-5α-4-azaandrostan-3-one 17β-(Isobutyloxycarbonyl-aminomethyl)-4-methyl-5α-4-azaandrost-1-en-3-one

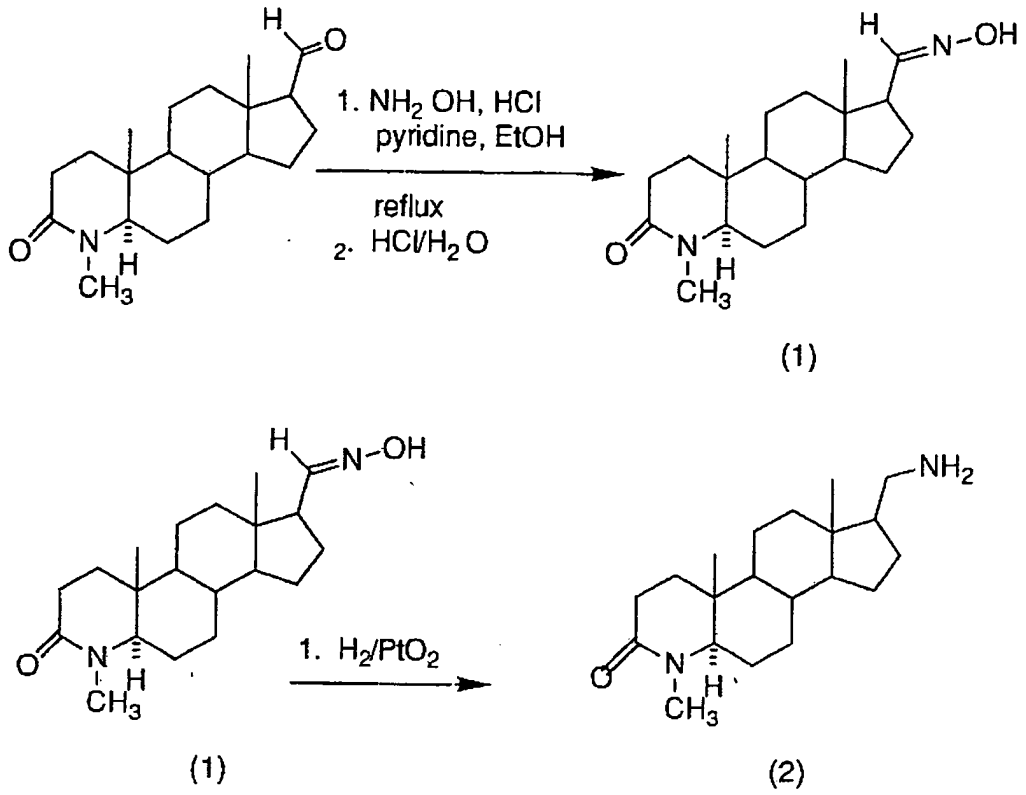
The following additional compounds may also be prepared according to the procedures described in the instant specification.

20-(Ethoxycarbonylamino)-4-methyl-5-α-4-azapregnan-3-one,
20-(Benzyloxycarbonylaminomethyl)-5–α-4-azapregnan-3-one,
4-Methyl-17ß-(N'-octadecylureidomethyl)-5–α-4-aza-androstan-3-one,
17ß-(N'-Benzylureidomethyl)-5–α-4-azaandrostan-3-one,
4-Methyl-17ß-(N'-methylureido)-5–α-4-azaandrostan-3-one,

4-Methyl-17ß-(Isobutyloxycarbonylamino)-5–α-4-aza-androstan-3-one,
17ß-(N'-(2-Ethylphenyl)ureidomethyl)-5–α-4-aza-androstan-3-one,
17ß-(N'-Allylureido)-4-methyl-5–α-4-azaandrostan-3-one,
20-(N'-(3-Chlorophenyl)ureido)-5–α-4-azapregnan-3-one,
4-Methyl-20-(N'-phenylureido)-5–α-4-azapregnan-3-one,
20-(N'-p-Tolylureidomethyl)-5–α-4-azapregnan-3-one,
17ß-(N'-(2,3-Dichlorophenyl)ureidomethyl)-4-methyl-5–α-4-azaandrostan-3-one,
17ß-(N'-(4-Fluorophenyl)ureido)-5–α-4-azaandrostan-3-one,
20-(N'-(2-Ethoxyphenyl)ureidomethyl)-4-methyl-5–α-4-aza-pregnan-3-one,
17ß-(N'-(3-Methoxyphenylureido)-5–α-4-azaandrostan-3-one,
4-Methyl-17ß-(N'-(naphth-2-yl)ureidomethyl)-5–α-4-azaandrostan-3-one,
4-Methyl-17ß-(N'-thiazol-2-ylureidomethyl)-5–α-4-aza-androstan-3-one,
4-Methyl-20-(N'-thien-2-ylmethylureido)-5–α-4-aza-pregnan-3-one,
17-(N'-(Adamant-1-yl)-thiouriedomethyl)-4-methyl-5-α-4-azaandrostan-3-one,
4-Methyl-17-N-(N'-4-(trifluoromethoxy)phenyl))-5-α-4-azaandrostan-3-one, and
17-((1-Adamantyloxy)-carbonylaminomethyl)-5-α-4-methyl-4-azaandrostan-3-one and the corresponding 1-en derivatives.

Synthesis of Testosterone 5α Reductase Inhibitors

Scheme 1 illustrates the synthesis of the intermediate oximes and amines used to produce compounds claimed in the instant invention.



SCHEME 1

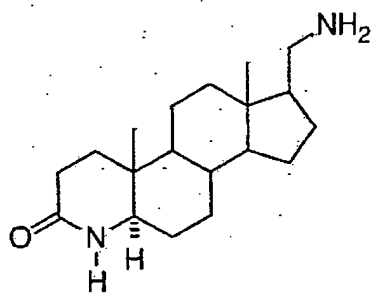
A stirred mixture of 4-methyl-3-oxo-5α-4-azaandrostan-17 carboxaldehyde, hydroxylamine hydrochloride, anhydrous pyridine, and anhydrous ethanol is refluxed gently under a nitrogen atmosphere for six to seven hours. After cooling, the ice-cooled mixture is diluted, with stirring, with a slight excess of chilled dilute hydrochloric acid. The suspension is then aged for about twenty minutes, filtered, washed with water and dried to give compound 1.

A mixture of the oxime (1), ethanol, glacial acetic acid and water is reduced in the presence of platinum oxide (PtO_2) until chromatographic analysis (TLC) indicates complete reduction to the

amine (2). The filtered reaction mixture is concentrated in vacuo; the resultant residue is dissolved in chloroform ($CHCl_3$) and washed with fresh dilute sodium hydrogen carbonate solution. The chloroform phase is then dried with sodium sulfate (Na_2SO_4). Concentration of the resultant $CHCl_3$ solution followed by trituration of the residue with hexane/ether will yield 2 as a white solid.

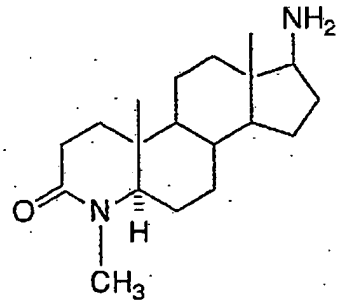
The following amines (3-9) may readily be prepared according to the above process to yield the indicated compounds:

3)



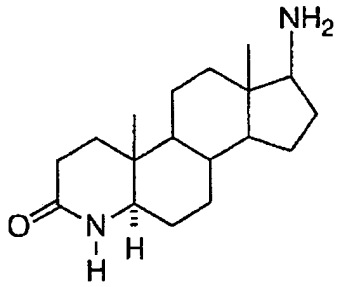
17-Aminomethyl-5-α-2-4-azaandrostan-3-one;

4)



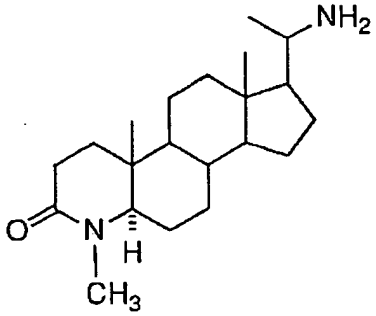
17-Amino-4-methyl-5-α-2-4-azaandrostan-3-one;

5)



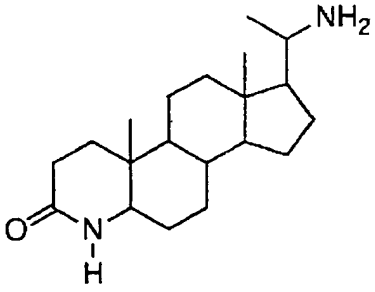
17-Amino-5-α-2-4-azaandrostan-3-one;

6)



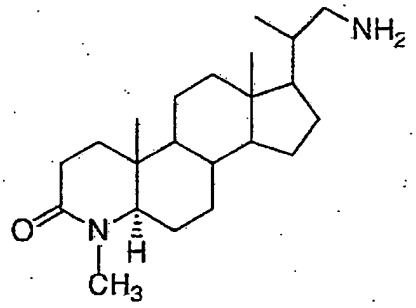
20-Amino-4-methyl-5-α-4-azapregnan-3-one;

7)



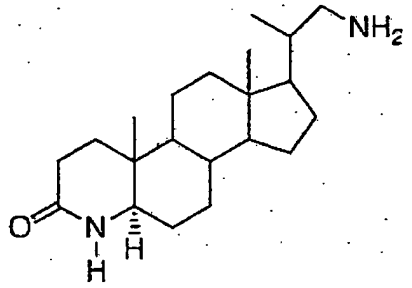
20-Amino-5-α-4-azapregnan-3-one;

8)



20-(Aminomethyl)-4-methyl-5-α–4-azapregnan-3-one;

9)

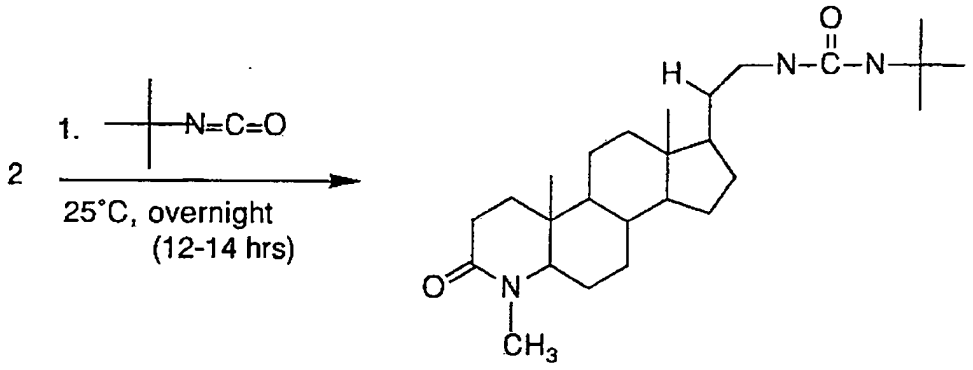


20-(Aminomethyl)-5-α–4-azapregnan-3-one;

As Scheme 1 indicates, the oximes useful as intermediates may readily be prepared by reacting a 4-azasteroidal aldehyde or ketone with hydroxylamine hydrochloride to form the corresponding oxime. The resultant oximes are subsequently reduced with hydrogen (H_2) and platinum oxide (PtO_2) or other suitable reducing agent to yield the respective amine. Product ureas or thioureas may be further alkylated with, for example, alkyl halides to give the corresponding R^2 alkylated compounds.

Scheme 2 illustrates the synthesis of the compound 17-(N'-t-butylureidomethyl)-4-methyl-5α-4-azaandrostan-3-one and is

representative of a basic synthesis of compounds claimed in the instant invention in which an amine is reacted with a substituted isocyanate.



(10)

SCHEME 2

To a stirred solution of compound 2 in dry benzene at room temperature (25°C) is added t-butylisocyanate or a suitable isocyanate. After stirring for 12-14 hours, the benzene is removed and the residue purified by flash chromatography (silica gel, EtOAc) to give 10 as a white solid. As Scheme 2 illustrates, 4-azasteroidal primary or secondary amines described in the instant invention are reacted with the desired substituted isocyanate, such as t-butyl isocyanate, to yield the target ureido derivative.

Representative substituted isocyanates include;

R^3-N=C=O

wherein R^3 equals

H,
C_{1-20} alkyl,
aryl,
heteroaryl,
arylC_{1-20}alkyl,
C_{3-20} cycloalkyl,
C_{3-20} cycloalkylC_{1-20}alkyl,

heteroarylC_{1-20}alkyl,
C_{2-20} alkenylC_{1-20}alkyl,
haloC_{1-20}alkyl,
C_{1-20} alkyloxyC_{1-20}alkyl,
C_{1-20} alkylcarbonylC_{1-20}alkyl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
hydroxyC_{1-20}alkyl,
arylC_{1-20}alkyloxyC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxyC_{1-20}alkyl,
arylcarbonylarylC_{1-20}alkyl,
diarylC_{1-20}alkyl,
triarylC_{1-20}alkyl,
C_{2-20} alkenyl,
C_{2-20} alkenylC_{1-20}alkyl,
C_{2-20} alkynylC_{1-20}alkyl,
arylC_{2-20}alkynylC_{1-20}alkyl,
heteroarylC_{2-20}alkynylC_{1-20}alkyl,
C_{1-20} alkylthioC_{1-20}alkyl,
C_{1-20} alkylsulfonylC_{1-20}alkyl, or
C_{1-20} alkylsulfinylC_{1-20}alkyl. R^3 is also selected from -t-butyl, 3-thienyl, -2-thienyl, -11-(isopropylthio)undecyl, -7-(carbomethoxy)heptyl, -(4-isobutylbenzene)ethyl, -7-(carboxy)heptyl, -acetylmethyl, -1-adamantylmethyl, -2-thienylmethyl, -2-(carbobenzyloxy)ethyl, -3,4 dimethoxyphenylmethyl, -phenyl, -5-bromopentyl, -11-hydroxyundecyl, -1(4-nitrophenyl)ethyl, -isopropylthiomethyl, -benzyloxymethyl, carbomethoxymethyl, -diphenylmethyl, -triphenylmethyl, -2-furyl, 4-isopropylphenyl, cyclohexylmethyl, 4-methylcyclohexyl, 3-(3-Indolyl)propyl, 3-Indoylmethyl, 4-isobutylbenzyl, 4-nitrobenzyl, 3-acetamidomethyl, 4-ethoxybenzyl, hexadecyl,

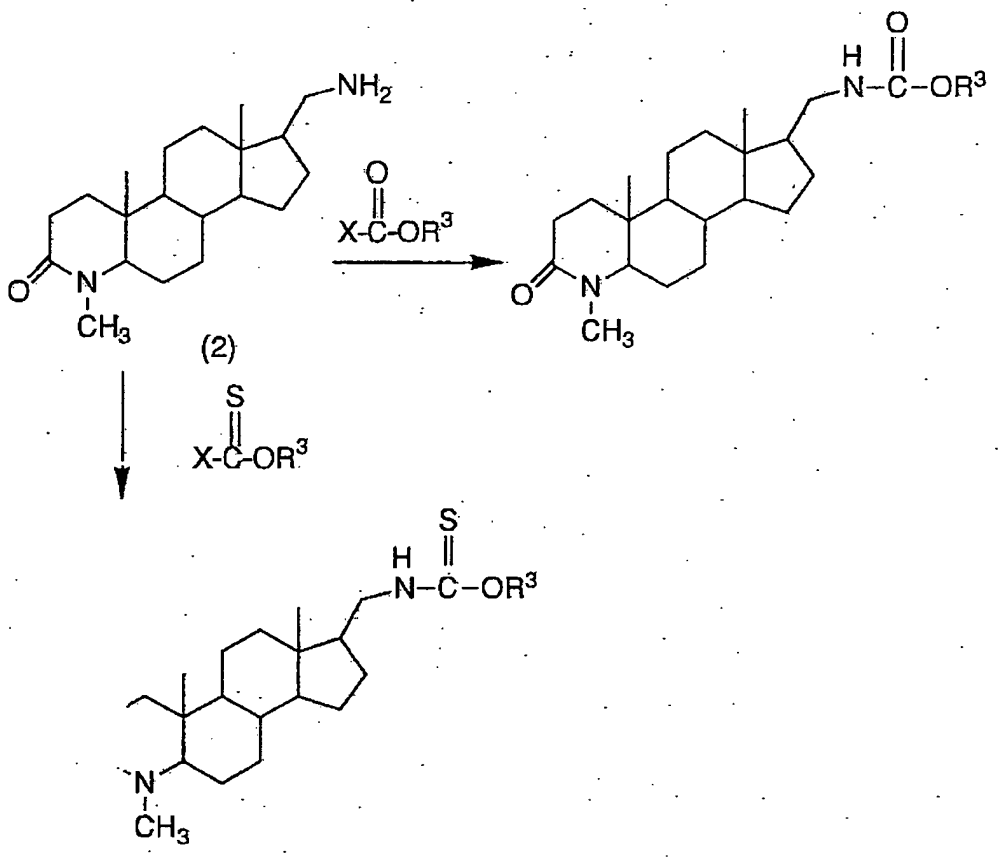
stearyl, 3,5 Bis(triflouromethyl), 3-cyanobenzyl, heptaflouropropyl, 4-benoylbenzyl, 5-benztriaoolyl, 3,5 diflourobenzyl, Bis (4-isopropylphenyl)methyl, 2 hydroxybenzyl, methyl, allyl, n-propyl, n-octyl, isopropyl, isobutyl, ethyl, benzyl, octadecyl, 2(ethyl)phenyl, 3(chloro)phenyl, 4(methyl)phenyl, 2,3(dichloro)phenyl, 4(flouro)phenyl, 3(methoxy)phenyl, 2(ethoxy)phenyl, 2(napthyl), or 2-thiazoyl or as specifically shown in the examples.

The primary or secondary amines disclosed in the instant invention may also be reacted with thioisocyanates of the formula

$$R^3\text{-}N{=}C{=}S$$

to yield compounds claimed in the instant invention. In addition, as Scheme 3 shows, the described primary or secondary amines disclosed in the invention (such as 2) may be reacted with activated esters or thioesters, e.g. chloro formates, to yield compounds claimed in the instant invention. R^3 is defined as above.

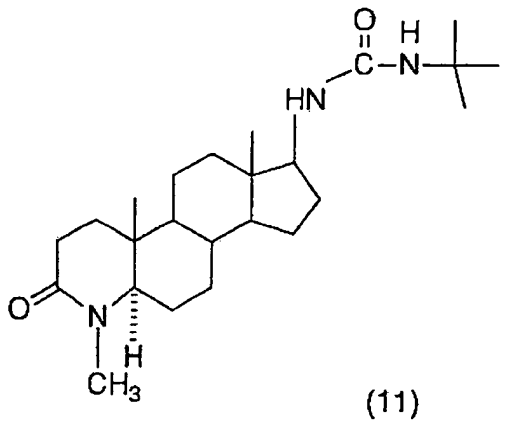
Substituted isocyanates or thioisocyanates may readily be prepared by known synthetic methods. For example, phosgene or thiophosgene may be reacted with a suitable primary amine to give a chloroformamide or chlorosulfamide which loses HCl to form the respective substituted isocyanate or thioisocyanate. For reviews of isocyanate and thioisocyanate preparation, see Patai, "The Chemistry of Cyanates and their thio Derivatives," pt 2, Wiley, New York, pp 619-818 and 1003-1221 (1977). In addition, many isocyanates, thioisocyanates, esters or thioesters used to prepare the claimed compounds are commercially available or readily prepared from commercially available compounds.



SCHEME 3

Ureas, thioureas, carbamates, and thiocarbamates claimed in the present invention may readily be obtained by following the basic procedure(s) described in Schemes 2 and 3. To further illustrate, compound 2 may be replaced by the amine (4) and reacted with t-butylisocyanate to yield 17-(N'-t-butylureido)-4-methyl-5α-4-azaandrostan-3-one (11) (Scheme 4).

(4) t-Butyl isocyanate

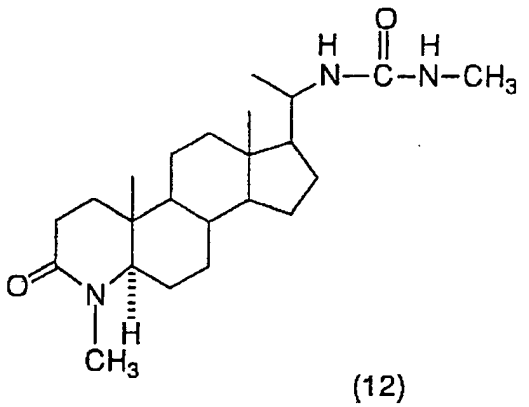


(11)

SCHEME 4

If compound 6 is reacted with methyl isocyanate under the conditions described for Scheme 2, 4-methyl-20-(N'-methylureido)-5α-4-azapregnan-3-one is obtained (12) (Scheme 5)

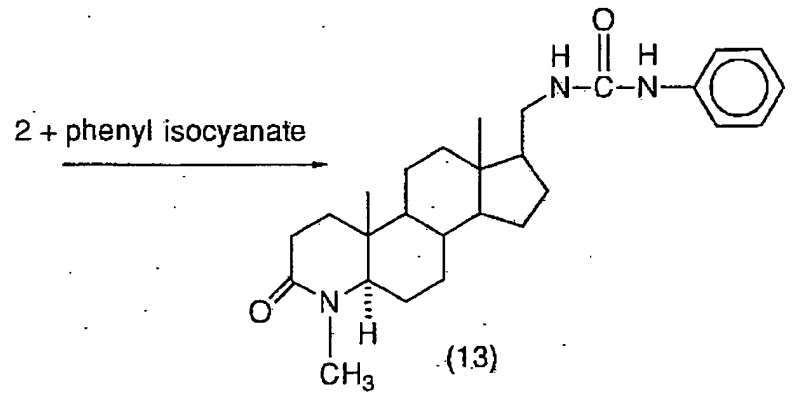
(6) + methyl isocyanate



(12)

SCHEME 5

If compound 2 is reacted with phenyl isocyanate under the conditions described in Scheme 2, 4-methyl-17-(N'-phenyluriedomethyl)-5α-4-azaandro-stan-3-one is made (13) (Scheme 6).

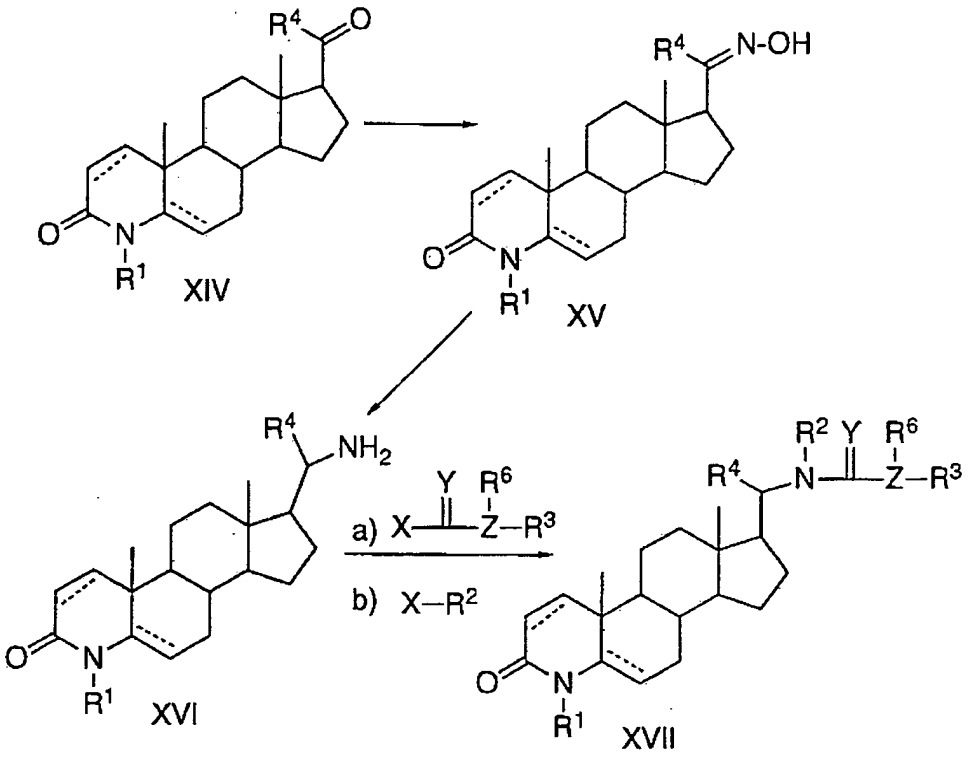


(13)

SCHEME 6

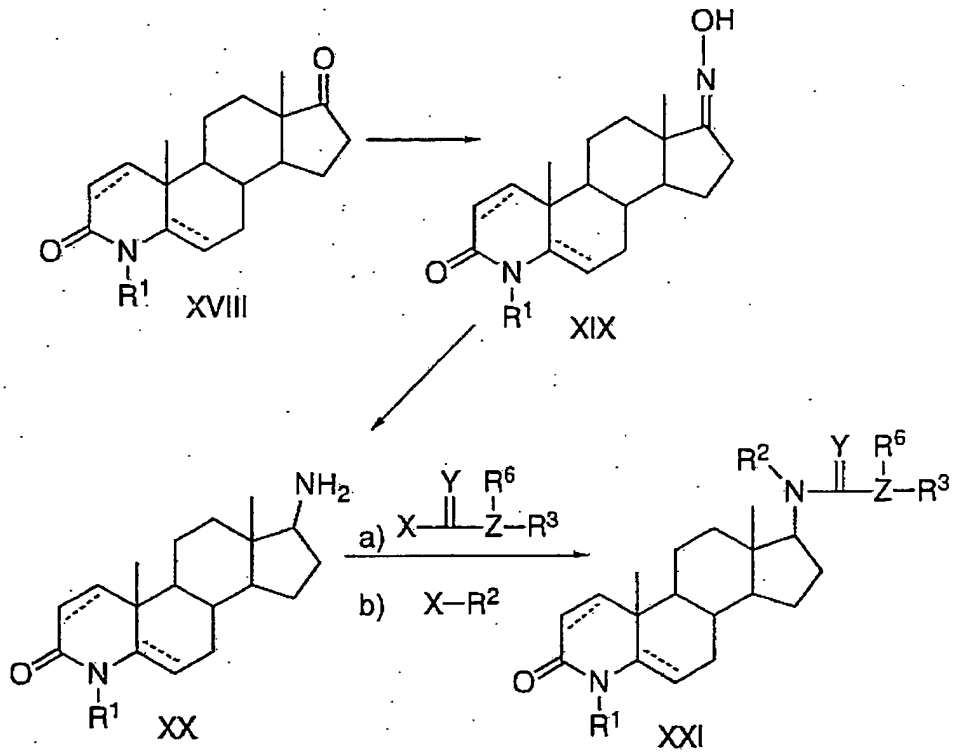
In addition, dehydrogenation of the 1,2 position may readily be accomplished by known synthetic methodology to produce the claimed 1-en derivatives. See U.S. 5,061,802 and Dolling et al., J. Am. Chem. Soc., 110, 3318-19 (1988).

Schemes 7,8 and 9 further illustrate how compounds claimed in the instant invention may be prepared. In Scheme 7, the starting 4-azasteroid aldehyde or ketone (XIV), obtained by known synthetic methods, is reacted to form the oxime XV; reduced to the amine XVI and reacted with a substituted isocyanate, substituted thioisocyanate, activated ester or thioester to form XVII.



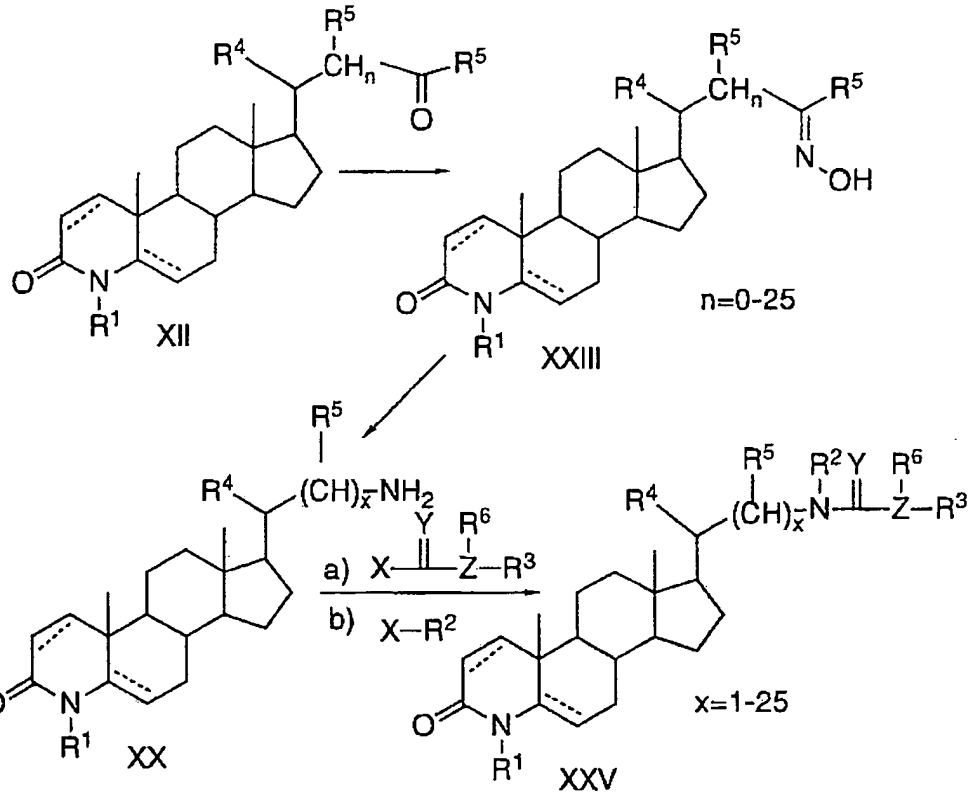
SCHEME 7

In Scheme 8, the identical procedure is followed using a generic 4-azasteroid (XVIII), prepared by known synthetic methods, to produce the oxime (XIX) which is reduced to the amine XX and reacted with a substituted isocyanate, substituted thioisocyanate, activated ester or thioester to form XXI.



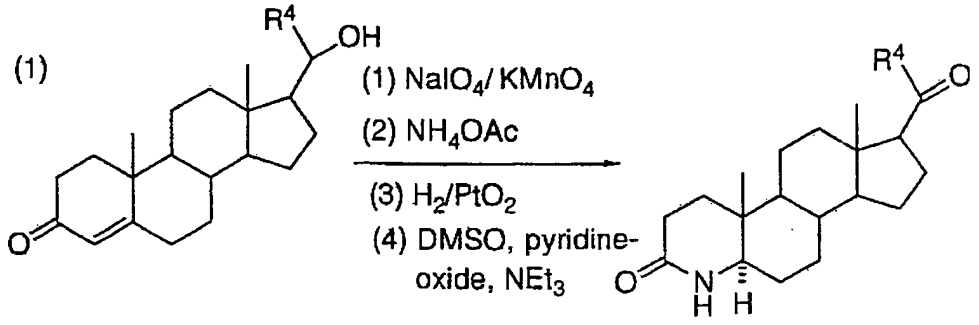
SCHEME 8

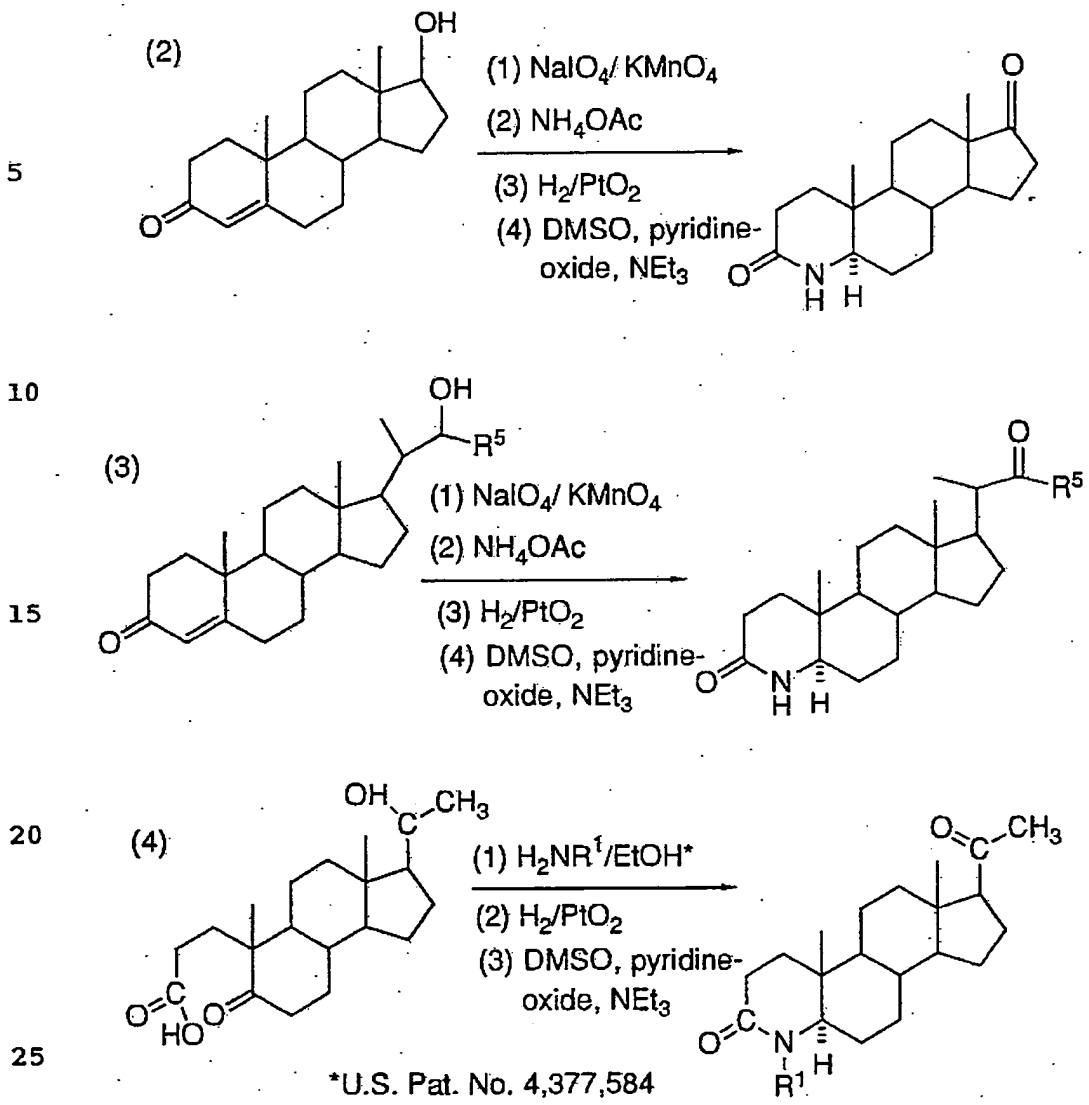
In Scheme 9, the generic 4-azasteroid XXII, also obtained from well known synthetic methodology, is reacted to form the oxime XXIII, which is further reduced to the amine XXIV, and reacted with a substituted isocyanate, substituted thioisocyanate, activated ester or thioester to form XXV.



SCHEME 9

The starting 4-azasteroidal ketones used in the present invention may be prepared according to the basic procedures described in Scheme 10 via well known synthetic methodology.





*U.S. Pat. No. 4,377,584

SCHEME 10

The following examples further describe the synthesis of compounds claimed in the instant invention.

Synthesis of Starting 4-Azasteroid Oximes:

EXAMPLE 1

1) 4-Methyl-3-oxo-5α-4-azaandrostan-17-carboxalde-hyde oxime

A stirred mixture of 4-methyl-3-oxo-5α-4-azaandrostan-17-carboxaldehyde (0.952 g, 3.0 mM), hydroxylamine hydrochloride (1.10 g, 15.8 mM), anhydrous pyridine (6 mL) and anhydrous ethanol (12 mL) was refluxed gently under a nitrogen atmosphere for 6.3 hours. After cooling, the ice-cooled mixture was diluted, with stirring, with a slight excess of chilled dilute hydrochloric acid (ca. 0.3 N), the suspension aged for ca. 20 minutes, filtered, washed with water and dried to give (1) 0.855 g. MS M^+ calcd for $C_{20}H_{32}N_2O_2$ 332.48, observed m/e 332.

Synthesis of Reactant 4-Azasteroid Amines:

EXAMPLES 2-9

2) 17-Aminomethyl-4-methyl-5α-4-azaandrostan-3-one

A mixture of (1) (0.67 g, 2.0 mM), ethanol (100 mL), glacial acetic acid (8 mL) and water (4 mL) was reduced in a hydrogen atmosphere (40 p.s.i.) at room temperature in the presence of PtO_2 until TLC analysis indicated complete reduction. The filtered reaction mixture was concentrated in vacuo, the residue taken up in chloroform, and the chloroform solution washed with fresh dilute sodium hydrogen carbonate solution and dried (Na_2SO_4). Concentration of the filtered chloroform solution followed by trituration of the residue obtained with hexane containing a small amount of ether yielded (2) as an off-white solid.

MS MH^+ calcd for $C_{20}H_{34}N_2O$ 318.49, observed m/e 319.

The following amines are representative of those obtained from the corresponding carbonyl compounds utilizing the above procedures:

3) 17-Aminomethyl-5α-4-azaandrostan-3-one.

4) 17-Amino-4-methyl-5α-4-azaandrostane-3-one.

5) 17-Amino-5α-4-azaandrostan-3-one.
6) 20-Amino-4-methyl-5α-4-azapregnan-3-one.
7) 20-Amino-5α-4-azapregnan-3-one.
8) 20-(Aminomethyl)-4-methyl-5α-4-azapregnan-3-one.
9) 20-(Aminomethyl)-5α-4-azapregnan-3-one.

Synthesis of Ureido 4-Azasteroids:

EXAMPLES 10-13

10) 17-(N'-t-Butylureidomethyl)-4-methyl-5α-4-aza-androstan-3-one

To a stirred solution of (2) (0.064 g, 0.2 mM) in dry benzene (8 mL) at room temperature was added t-butyl isocyanate (0.035 mL, 0.3 mM) dropwise over ca. 0.5 min. After stirring overnight the benzene was removed in vacuo and the residue flash chromatographed (silica gel, ethyl acetate as eluant) to give (10) as a white solid.

MS M^+ calcd for $C_{25}H_{43}N_3O_2$ 417.64, observed m/e 417.

11) 17-(N'-t-Butylureido)-4-methyl-5α-4-azaandro-stan-3-one

When (2) in the above example was replaced by (4), (11) was obtained as a white solid.

MS M^+ calcd for $C_{24}H_{41}N_3O_2$ 403.61, observed m/e 405.

12) 4-Methyl-20-(N'-methylureido)-5α-4-azapregnan-3-one

When (6) was reacted with methyl isocyanate under the conditions of Example (10), (12) was obtained as a white waxy solid.

MS M^+ calcd for $C_{23}H_{39}N_3O_2$ 389.58, observed m/e 389.

13) 4-Methyl-17-(N'-phenylureidomethyl)-5α-4-azaandrostan-3-one

When (2) was reacted with phenyl isocyanate under the conditions of Example (10), (13) was obtained as a white solid.

MS MH^+ calcd for $C_{27}H_{39}N_3O_2$ 437.40, observed m/e 438.

Examples 14-21 prepared according to the basic procedures described above further exemplify the claimed invention.

14) 4-Methyl-17ß-(N'-n-propylureidomethyl)-5α-4-azaandro-stan-3-one
MS MH^+ calc. for $C_{24}H_{41}N_3O_2$ 403.40, observed m/e 404.

15) 4-Methyl-17ß-(N'-n-octylureidomethyl)-5α-4-azaandrostan-3-one
MS MH^+ calc. for $C_{29}H_{51}N_3O_2$ 473.49, observed m/e 474.

16) 4-Methyl-17ß-(N'-phenylureido)-5α-4-azaandro-stan-3-one
MS MH^+ calc. for $C_{26}H_{37}N_3O_2$ 423.52, observed m/e 424.

17) 17ß-(N'-Isopropylureidomethyl)-4-methyl-5α-4-aza-androstan-3-one
MS MH^+ calcd for $C_{24}H_{41}N_3O_2$ 403.61 observed m/e 404.

18) 20-(N'-t-Butylureidomethyl)-4-methyl-5α-4-aza-pregnan-3-one
MS MH^+ calcd for $C_{27}H_{47}N_3O_2$ 445.35, observed m/3 446.

19) 20-((Iminodibenz-5-yl)carbonylaminomethyl)-4-methyl-5α-4-azapregnan-3-one
MS MH_2^{++} calcd. for $C_{37}H_{49}N_3O_2$ 567.82, observed m/e 569.

20) 17ß-((Iminodibenz-5-yl)carbonylaminomethyl)-4-methyl-5α-4-azaandrostan-3-one
MS MH_2^{++} calcd.for $C_{35}H_{45}N_3O_2$ 539.74, observed m/e 541.

21) 17ß-((Isobutyloxycarbonylaminomethyl)-4-methyl-5α-4-azaandrostan-3-one
MS MH^+ calcd. for $C_{25}H_{42}N_2O_3$ 418.62, observed m/e 419.

Table 2 illustrates the NMR data of the above examples.

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TABLE 2
NMR DATA (ppm)

Example	Angular Methyls	Miscellaneous
10	0.66, 0.86	1.33 (-NHCONH-C(C<u>H</u>3)3)
11	0.67, 0.88	1.33 (-NHCONH-C(C<u>H</u>3)3)
12	0.73, 0.88	2.92 (-4-NC<u>H</u>3)
13	064, 0.86	2.92 (-4-NC<u>H</u>3)
14	0.64, 0.88	2.90 (-4-NC<u>H</u>3)
16	0.63, 0.86	2.93 (-4-NC<u>H</u>3)
17	0.66, 0.88	1.12 (-NH-CH(C<u>H</u>3)2 1.16
18	0.64, 0.85	1.29 (-NHCONH-C(C<u>H</u>3)3)
19	0.62, 0.89	0.82-CH(C<u>H</u>3)CH2NHCON- 0.86
20	0.61, 0.88	2.92 (-4-NC<u>H</u>3)
21	0.66, 0.88	2.92 (-4-NC<u>H</u>3)

In addition to the compounds described above the following compounds were also prepared according to the processes described in the specification:
17β-(N'(Adamant-1-yl)thioureidomethyl)-4-methyl-5-α-4-azaandrostan-3-one,
17β-((1-Adamantyloxy)-carbonylaminomethyl)-5-α-4-methyl-4-azaandrostan-3-one, and
4-Methyl-17β-(N'-(4-(trifluromethoxy)phenyl))-5-α-4-azaandrostan-3-one. The 1-en-3-one compounds of each of the above examples and of the claimed compounds may readily be prepared according to well known synthetic processes.

The above examples are non-limiting and suitable acylating agents, isocyanates, or thioisocyanates may readily be substituted

according to the methods described in the present invention and reacted with a described azasteroidal amine to form the claimed ureas, thioureas, carbamates, and thiocarbamates. The following definitions further clarify the present invention.

The term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds of this invention which are generally prepared by the free base with a suitable organic or inorganic acid. Representative salts include the following salts: Acetate, adipate, alginate, aspartate, benzenesulfonate, benzoate, bicarbonate, bisulfate, borate, butyrate, camsylate, carbonate, camphorate, chloride, citrate, fumarate, glucoheptanate, gluconate, glutamate, glycerolphosphate, hydrobromide, hydrochloride, hydroiodide, lactate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate. The invention further relates to all stereoisomers, diastereomers or enantiomers of the compounds depicted.

The term "pharmaceutically effective amount" shall mean that amount or quantity of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by a reseacher or clinician or physician.

The term "aryl" shall mean a mono- or polycyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is defined as H, C_{1-6} alkyl or arylC_{1-20}alkyl wherein said alkyl groups are unsubstituted or substituted with C_{1-8} alkyloxy, amino, mono- and di -C_1-C_4 alkylamino, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfinyl, carboxyC_{1-10}alkyl, hydroxy, or halogen. The term "aryl" also encompasses those aromatic systems which independently have C_{1-20}alkyl, hydroxyl, C_{1-20} alkyloxy, haloC_{1-20}alkyl, benzoyl, cyano, nitro, carboxamido, acetamido, C_{2-20}alkenyl and halogens directly bonded to the aromatic carbon atom(s) or as further defined in the specification. The term aryl specifically includes phenyl, napthyl, and anthrancenyl or biphenyl.

The term "heteroaryl" shall mean a mono- or polycyclic system composed of 5- and 6-membered aromatic rings containing 1,2,3

or four heteroatoms chosen from N,O, or S and either unsubstituted or substituted with R as defined above or with hydroxyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, haloC_{1-20}alkyl, benzoyl, cyano, nitro, carboxamido, acetamido and halogens directly bonded to the aromatic carbon atoms. The term heteroaryl is further defined to include heterocyclic species such as 5-7-membered monocyclic rings which are either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring so that a portion of the molecule is aromatic. Examples of heterocyclic species or elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrinidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiszolyl, quinuclidinyl, isothiszolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thisdiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Preferred embodiments clearly include those heteroaryl and heterocyclic species depicted in the specific examples.

The term "alkyl" shall mean straight or branched chain alkane.

The term "alkenyl" shall mean straight or branched chain alkene.

The term "alkynyl" shall mean straight or branched chain alkyne.

The term "arylalkyl" shall be taken to include an aryl portion as defined above and an alkyl portion as defined above.

The term "heteroarylalkyl" shall mean an heteroaryl portion as defined above and an alkyl portion as defined above.

The "C_{1-n}" designation where n may be an integer from 1 to 20 or 2-20 respectively refers to an alkyl group or substituent and to the alkyl portion of an arylalkyl or heteroarylalkyl unit. In addition, it refers to cycloalkyl substituents and alkenyl, aryl or alkynyl groups.

The term "halogen" shall include fluorine, chlorine, iodine and bromine.

The term "oxy" shall mean an oxygen (O) atom.

The term "thio" shall mean a sulfur atom.

In the schemes and examples described in this disclosure, various reagent symbols have the following meanings:

PtO_2 is platinum oxide

TLC is thin layer chromatography

Na_2SO_4 is sodium sulfate

DMAP is 4-(dimethylamino)pyridine

DCC is N,N'-dicyclohexylcarbodiimide

The previous examples are illustrative of representative embodiments of this invention and should not be construed to be limits on the scope or spirit of the instant invention.

The Rf values cited were carried out on standard thin layer chromatographic silica gel plates. The elution solvent system used is given in the parentheses following the Rf value.

The mass spectral values are given either as FAB, i.e., fast atom bombardment, or electron impact (EI) and are reported as molecular ion peaks, either being (M), (M+1) or (M+2), the molecular weight, MW, or the MW plus one or two atomic units.

The nuclear magnetic resonance data was taken at 200 or 400 MHz in $CDCl_3$ and is tabulated for unique proton values of each compound at the end of the Examples.

Also included within the scope of this invention are 4-N-X analogs where X is OH, NH_2 or SCH_3. The 4-N-OH and 4-N-NH_2

derivatives can be made by incorporating hydroxylamine or hydrazine, respectively, in place of methylamine in the seco acid ring A closure for the starting androstanes herein described in J. Med. Chem. 29, 2998-2315 (1986) by Rasmusson et al. Futher, reaction of the anion of the saturated 4-N-H adrostanes, wherein the anion is generated from the 4-N-H precursor by sodium hydride, and methylsulfenyl chloride can produce the corresponding 4-N-S-CH_3 derivetive. Thus, substituent R or the 4-N position also include, OH, NH_2 and S-CH_3.

The present invention has the objective of providing suitable topical, oral and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention.

The compositions containing the compounds of the present invention as the active ingredient for use in the treatment of e.g., benign prostatic hypertrophy, prostatitis, and treatment and prevention of prostatic carcinoma, hyperandrogenic conditions, can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration, as, for example, by oral administration in the form of tablets, capsules, solutions, or suspensions, or by injection. The daily dosage of the products may be varied over a wide range varying from 0.5 to 1,000 mg per adult human/per day. The compositions are preferably provided in the form of scored tablets containing 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.002 mg. to about 50 mg./kg. of body weight per day. Preferably the range is from about 0.01 mg. to 7 mg./kgs. of body weight per day. These dosages are well below the toxic dose of the product. For the treatment of androgenic alopecia, acne vulgaris, seborrhea, female hirsutism, the compounds of the present invention are administered in a pharmaceutical composition comprising the active compound in combination with a pharmacologically acceptable carrier adapted for topical, oral or parenteral administration.

These topical pharmaceutical compositions may be in the form of a cream, ointment, gel or aerosol formulation adapted for application to the skin. These topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.1% to 15%, preferably about 5%, of the active compound, in admixture with about 95% of vehicle.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a 5 α–reductase agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

Oral dosages of the present invention, when used for the indicated effects, will range between about Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use

of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, zanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present

invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl- methacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

BIOLOGICAL ASSAYS

Preparation of Human prostatic and scalp 5a-reductases.

Samples of human tissue were pulverized using a freezer mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethyl-sulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500xg for 15 min. The crude nuclear pellet was washed two times and resuspended in two volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic and scalp reductases were stable for at least 4 months when stored under these conditions.

5α-reductase assay.

The reaction mixture contained in a final volume of 100 µl is: 40 mM buffer (human scalp, potassium phosphate, pH 6.5; human prostatic 5α-reductase, sodium citrate, pH 5.5), 0.3-10 µM ^{14}C-T (or ^{3}H-T), 1 mM DTT, and 500 µM NADPH. Typically, the assay was initiated by the addition of 50-100 µg prostatic homogenate or 75-200 µg scalp homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250 µl of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10 µg each DHT and T. The

aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase HPLC (10 cm Whatman partisil 5 silica column equilibrated in 1 ml/min 70 % cyclohexane: 30 % ethyl acetate; retention times DHT, 6.8-7.2 min; androstanediol, 7.6-8.0; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655A autosampler, Applied Biosystems Model 757 variable UV detector, and a Radiomatic Model A120 radioactivity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo Scint 1 (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids observed with the human prostate and scalp preparations were T, DHT and androstanediol.

Stumptail macaque protocol

The following protocol is utilized with the stumptail macaque monkey to demonstrate the effect of compounds of the present invention for promoting hair growth.

Twenty-one male stumptail macaque monkeys of species *Macaca speciosa* are assigned to vehicle control and drug treatment groups on the basis of baseline hair weight data. This assignment procedure is necessary to insure that the average baseline hair growth for each control and experimental group is comparable. The control and drug treatment groups are as follows:

1. Topical 50:30:20 vehicle (N = 6)
2. Oral 5α-reductase and topical 50:30:20 vehicle (N = 5)
3. Oral placebo (N = 5)
4. 5α-reductase in vehicle (N = 5)

The vehicle consists of 50% propylene glycol, 30% ethanol and 20% water. A 100 mM concentration of topical 5α-reductase is formulated in this vehicle. The same 5α-reductase is administered as an oral dose of

0.5mg per monkey. Immediately prior to the dosing phase of the study, hair is removed from a 1 inch square area (identified by four tatoos) in the center of the balding scalp. This hair collection is the baseline hair growth determination prior to the beginning of treatment. Approximatly 250μL of vehicle and 5α-reductase in vehicle is prepared and topically administered to the tatooed area of the scelp. The selected 5α-reductase and placebo is ingested by the monekys at the same time as the topical doses are administered. The monkeys are dosed once per day, seven days per week for twenty weeks.

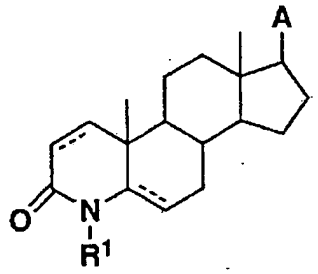
At four week intervals throughout the dosing phase of the study, each monkey is shaved and the hair is collected and weighed. The body weight data (at baseline and during assay) is analyzed by the nonparametric Wilcoxon rank-sum test. Differences are significant at $p < 0.05$. Hair weight data at each week collection for vehicle, placebo and treatment groups are expressed as the change from baseline. Statistical analysis is performed on the rank of the data to show overall differences among groups at each four week collection.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of

the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

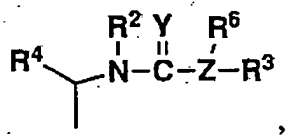
1. A compound of the formula:



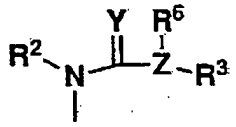
I

and the pharmaceutically acceptable salts thereof, wherein:

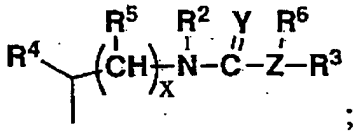
A is:



(a) ,



(b) except when R^2 equals H, Y equals O, Z equals N and there is a 5αH, R^6 and R^3 cannot be independently selected from H, C_{1-8} alkyl, C_{3-6} cycloalkyl, phenyl or when R^6 and R^3 are taken together with the adjacent N to form a 5-6 membered ring comprising up to one other heteroatom selected from O or N, or



(c) ; wherein

R^1 is:

H, methyl or ethyl;

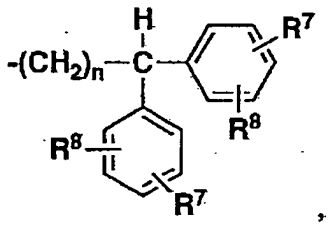
R^2 is:

H, or
C_{1-20} alkyl;

R^3 is:

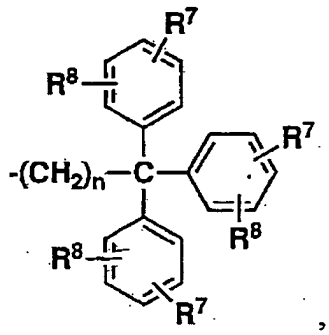
H,
amino,
mono C_1-C_4alkylamino,
di C_1-C_4alkylamino,
mono C_1-C_4 alkylaminoaryl,
di C_1-C_4 alkylaminoaryl,
C_{1-20} alkyl,
C_{6-14} aryl,
heteroaryl,
C_{6-14} arylC_{1-20}alkyl,
C_{3-20}cycloalkyl,
C_{3-20}cycloalkylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{2-20} alkenylC_{1-20}alkyl,
haloC_{1-20}alkyl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
C_{1-20}alkyloxyC_{1-20}alkyl,
carboxylC_{1-20}alkyl,
C_{6-14} arylcarbonylC_{6-14}arylC_{1-20}alkyl,
C_{1-20}alkylcarbonylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
hydroxylC_{1-20}alkyl,
halohydroxylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxyC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxyC_{1-20}alkyl,

carboxylC1-20alkyl,
C1-20alkylcarbonylC1-20alkyl,
thiosulfatoC1-20alkyl,
diarylC1-20alkyl of the formula:



, n equals 0-19;

triarylC1-20alkyl of the formula:



, n equals 1-19;

C2-20 alkenyl,
C2-20 alkenylC1-20alkyl,
C2-20alkynylC1-20alkyl,
C6-14 arylC2-20alkynylC1-20alkyl,
heteroarylC2-20alkynylC1-20alkyl,
C1-20alkylthioC1-20alkyl,
C1-20alkylsulfonylC1-20alkyl, or
C1-20alkylsulfinylC1-20alkyl;

R^4 is:

H,
C1-20 alkyl,

C_6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen; or
heteroaryl;

R^5 can be the same or different when x is greater than 1 and is:
H, or
C_{1-12} alkyl,
heteroaryl, or
C_{6-14} aryl;

R^6 is present when Z equals N and is independently
H,
C_{1-20} alkyl, or
equivalent to R^3; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

R^7 or R^8 are:

H,
CH_3,
C_2H_5,
carboxamido,
OH,
OCH_3,
NO_2,
CN,

F,
RS,
RSO,
RSO_2,
R_2N, where R can be the same or different selected from H, C_1-C_4 alkyl, or C_6-C_{10} aryl;
Cl,
acetamido,
OC_2H_5,
CF_3,
isopropyl, or
isobutyl; n equals 1-10 and the C_{1-20}alkyl portion is optionally substituted with R^5;

Y is:

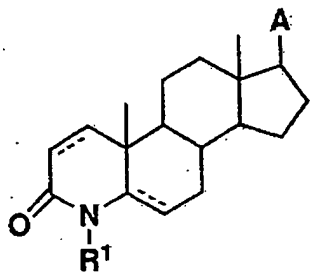
O, or
S;

Z is:

N, or
O;

x is an integer from 1-25 and dashes indicate a double bond is optionally present.

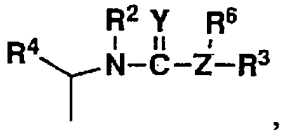
2. A compound of the formula:

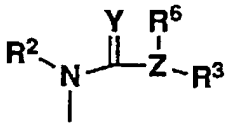


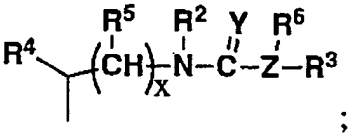
I

and the pharmaceutically acceptable salts thereof, wherein:

A is:

(a)  ,

(b)  except when R^2 equals H, Y equals O, Z equals N and there is a 5αH, R^6 and R^3 cannot be independently selected from H, C_{1-8} alkyl, C_{3-6} cycloalkyl, phenyl or when R^6 and R^3 are taken together with the adjacent N to form a 5-6 membered ring comprising up to one other heteroatom selected from O or N, or

(c)  ; wherein

R^1 is:

H, methyl or ethyl;

R^2 is:

H, or
C_{1-20} alkyl;

R^3 is:

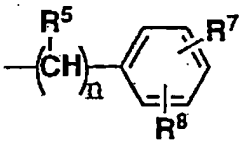
H,

C_{1-20}alkyl is a straight or branched chain alkane of up to 20 carbon atoms;

C_{6-14} aryl wherein aryl is a mono or polycyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamido or halogen;

heteroaryl which is a mono or polycyclic system composed of 5- or 6-membered aromatic rings consisting of 1,2, 3 or 4 heteroatoms chosen from N, O, or S and either unsubstituted or substituted with R or independently with hydroxyl, C_{1-20}alkyloxy, C_{1-20}alkyl, benzoyl, carboamide, acetamide, halogens, C_{2-20}alkenyl, cyano, nitro, or haloalkyl directly bonded to the aromatic carbon atoms(s);

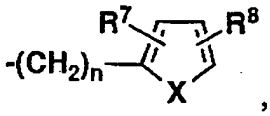
C_{6-14} arylC_{1-20}alkyl of the formula:



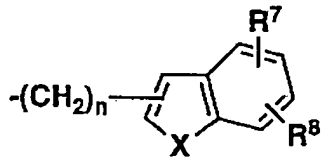
wherein the aromatic ring is optionally and independently substituted with R^7 and R^8 wherein R^7 and R^8 are
H,
CH_3,
C_2H_5,
carboxamido,

OH,
OCH_3,
NO_2,
CN,
F,
RS,
RSO,
RSO_2,
R_2N, where R can be the same or different selected from H, C_1-C_4 alkyl, or C_6-C_{10} aryl;
Cl,
acetamido,
OC_2H_5,
CF_3,
isopropyl, or
isobutyl; n equals 1-10 and the C_{1-20}alkyl portion is optionally substituted with R^5;

HeteroarylC$_{1-20}$alkyl of the formula:



, or



wherein X equals O, S, or NR; and n equals 1-20;

C_{1-20}alkylsulfonylC_{1-20}alkyl,
C_{1-20}alkylthioC_{1-20}alkyl,
C_{1-20}alkylsulfinylC_{1-20}alkyl of the formula:

$-(CH_2)_nS(O)_p-R^9$ wherein R^9 is

CH_3,
C_2H_5,
C_3H_7,
C_4H_9,
isopropyl,
isobutyl,
sec-butyl,
t-butyl,
isopentyl,
neopentyl, or
ixohexyl; n equals 1-15 and p=0-2;

$C_{1\text{-}20}$alkyloxycarbonyl$C_{1\text{-}20}$alkyl of the formula:

$-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR^{10}$ wherein R^{10} is:
CH_3,
C_2H_5,
C_3H_7,
C_4H_9, or
C_5H_{11}; and n equals 1-20;

Carboxyl$C_{1\text{-}20}$alkyl of the formula:

$-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OH$; n = 1-20;

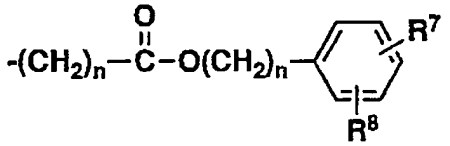
$C_{1\text{-}20}$alkylcarbonyl$C_{1\text{-}20}$alkyl of the formula

$-(CH_2)_n-\overset{O}{\overset{\|}{C}}-(CH_2)_m CH_3$, n equals 1-20;
m equals 0-19;

$C_{3\text{-}20}$cycloalkyl$C_{1\text{-}20}$alkyl of the formula:

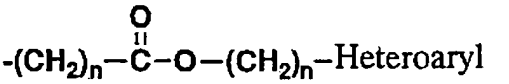
-$(CH_2)_n$-(cycloalkyl) wherein the cycloalkyl protion is a monocyclic, bicyclic, or polycyclic hydrocarbon of up to 20 carbon atoms wherein the rings are optionally substituted with R^1; and n = 1-20;

ArylC1-20alkyloxycarbonylC1-20alkyl of the formula:



wherein R^7 and R^8 are as defined; n equals 1-20;

HeteroarylC1-20alkyloxycarbonylC1-20alkyl of the formula:



wherein Heteroaryl is as defined and n = 1-20;.

haloC1-20 alkyl of the formula:

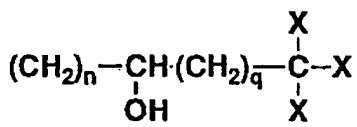
$-(CH_2)_n-CH_2X$ wherein

X equals Br, Cl, F or I; n is 1-19;

hydroxylC1-20alkyl of the formula:

$-(CH_2)_nCH_2OH$; n is 1-19;

halohydroxylC1-20alkyl of the formula:



wherein

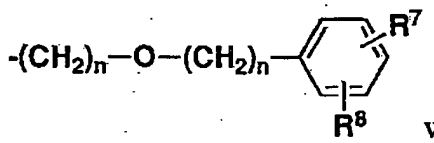
n = 1-18

q = 0-18

n + q = 0-18 and

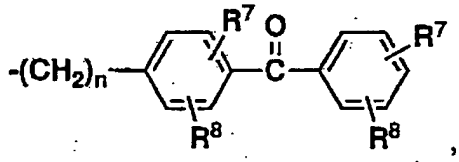
X equals Br, Cl, F or I;

$C_{6-14}Aryl C_{1-20}alkyloxy C_{1-20}alkyl$ of the formula:



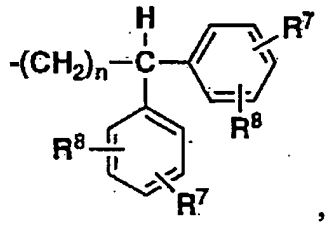
wherein R^7 and R^8 are as defined; n is 1-20;

ArylcarbonylarylC_{1-20}alkyl of the formula:



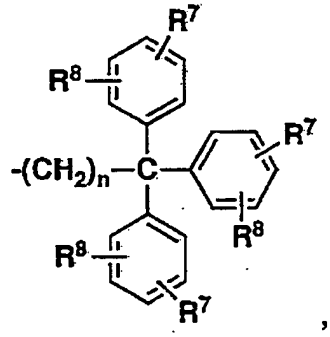
, n equals 1-20;

DiarylC_{1-20}alkyl of the formula:



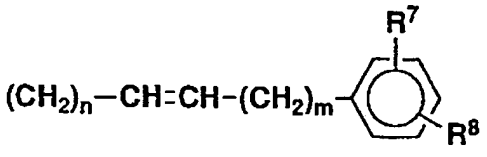
, n equals 0-19;

TriarylC_{1-20}alkyl of the formula:



, n equals 1-19;

Aryl C_{2-20}alkenyl of the formula:



n = 0-18
m = 0-18
m+n = 0-18

R^4 is

H,
C_{1-20}alkyl,
C_6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen; or

heteroaryl;

R^5 can be the same or different when x is greater than one and is;
H, or
C_{1-12}alkyl;

R^6 is present when Z equals N and is independently
H,
C_{1-20} alkyl, or

equivalent to R^3; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

Y is:

O, or
S;

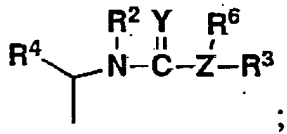
Z is:

N, or
O;

x is an integer from 1-10 and dashes indicate a double bond is optionally present.

3. A compound according to Claim 1 and the pharmaceutically acceptable salts thereof, wherein:

A is:



; wherein

R^1 is:

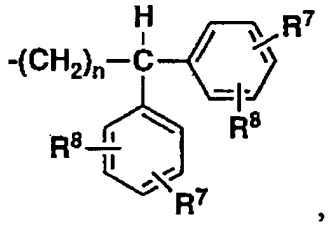
H, methyl or ethyl;

R^2 is:

H, or
C_{1-20} alkyl;

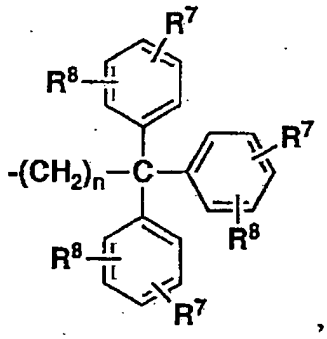
R^3 is:

H,
C_{1-20} alkyl,
C_{6-14} arylC_{1-20}alkyl,
C_{3-20}cycloalkyl,
C_{3-20}cycloalkylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{1-20}alkylcarbonylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
carboxylC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
hydroxylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxyC_{1-20}alkyl,
heteroaryl,
C_{6-14} aryl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
C_{2-20} alkenylC_{1-20}alkyl,
C_{1-20}alkyloxyC_{1-20}alkyl,
C_{6-14} arylcarbonylC_{6-14}arylC_{1-20}alkyl,
halohydroxylC_{1-20}alkyl,
diarylC_{1-20}alkyl of the formula:



, n equals 0-19;

triarylC_{1-20}alkyl of the formula:



, n equals 1-19;

halo C1-20alkyl,
C1-20alkylxoyC1-20alkyl,
C1-20alkylthioC1-20alkyl,
C1-20alkylsulfonylC1-20alkyl, or
C1-20alkylsulfinylC1-20alkyl;

R^4 is:

H,
C1-20 alkyl,
heteroaryl, or

C6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C1-6 alkyl, arylC1-20alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C1-8alkyloxy, carboxy C0-10alkyl, or halogen or aryl directly substituted independently with amino, mono C1-C4 alkylamino, di C1-C4 alkylamino, mono C1-C4 alkylaminoaryl, di C1-C4 alkylaminoaryl, hydroxyl, haloC1-20alkyl, carboxamido, benzoyl, C1-20alkyloxy, C1-20alkyl, C2-20alkenyl, cyano, nitro, acetamide or halogen;

R^6 is present when Z equals N and is independently

H,
C1-20 alkyl, or
equivalent to R^3; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

R^7 or R^8 are:

H,
CH_3,
C_2H_5,
carboxamido,
OH,
OCH_3,
NO_2,
CN,
F,
RS,
RSO,
RSO_2,
R_2N, where R can be the same or different selected fromH, C_1-C_4 alkyl, or C_6-C_{10} aryl;
Cl,
acetamido,
OC_2H_5,
CF_3,
isopropyl, or
isobutyl; n equals 1-10 and the C_{1-20}alkyl portion is optionally substituted with R^5;

Y is:

O, or
S;

Z is:

N, or
O.

4. A compound according to Claim 3 and the pharmaceutically acceptable salts thereof, wherein:

R^1 is:

H,
CH_3, or
C_2H_5;

R^2 is:

H,
CH_3,
C_2H_5, linear or branched:
C_3H_7,
C_4H_9,
C_5H_{11},
C_6H_{13}, or
C_7H_{15};

R^3 is:

-t-butyl,
3-thienyl,
-2-thienyl,
-11-(isopropylthio)undecyl,
-7-(carbomethoxy)heptyl,
-(4-isobutylbenzene)ethyl,
-7-(carboxy)heptyl,
-acetylmethyl,
-1-adamantylmethyl,
-2-thienylmethyl,
-2-(carbobenzyloxy)ethyl,
-3,4 dimethoxyphenylmethyl,

-phenyl,
-5-bromopentyl,
-11-hydroxyundecyl,
-1(4-nitrophenyl)ethyl,
-isopropylthiomethyl,
-benzyloxymethyl,
carbomethoxymethyl,
-diphenylmethyl,
-triphenylmethyl,
-2-furyl,
4-isopropylphenyl,
cyclohexylmethyl,
4-methylcyclohexyl,
3-(3-Indolyl)propyl,
3-Indoylmethyl,
4-isobutylbenzyl,
4-nitrobenzyl,
3-acetamidomethyl,
4-ethoxybenzyl,
hexadecyl,
stearyl,
3,5 Bis(triflouromethyl),
3-cyanobenzyl,
heptaflouropropyl,
4-benoylbenzyl,
5-benztriaoolyl,
3,5 diflourobenzyl,
Bis (4-isopropylphenyl)methyl,
2 hydroxybenzyl,
methyl,
allyl,
n-propyl,
n-octyl,
isopropyl,

isobutyl,
ethyl,
benzyl,
octadecyl,
2(ethyl)phenyl,
3(chloro)phenyl,
4(methyl)phenyl,
2,3(dichloro)phenyl,
4(flouro)phenyl,
3(methoxy)phenyl,
2(ethoxy)phenyl,
2(napthyl), or
2-thiazoyl;

R^4 is:

H,
methyl,
ethyl,
linear or branched:
propyl,
butyl,
C_6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen, or
heteroaryl;

R^6 is present when Z equals N and is independently
H,
C_{1-20} alkyl, or
equivalent to R^3; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

Y is:

O, or
S;

Z is:

N, or
O.

5. The compound according to Claim 4 and the pharmaceutically acceptable salts thereof, wherein the compound is selected from:

17ß-(N'-t-Butylureidomethyl)-4-methyl-5-α–4-azaandrostan-3-one,

4-Methyl-17ß-(N'-phenylureidomethyl-5α-4-azaandrostan-3-one,

4-Methyl-20-(N'-methylureido)-5α-4-azapregnan-3-one,

4-Methyl-17ß-(N'-n-propylureidomethyl-5-α–4-azaandrostan-3-one,

4-Methyl-17ß-(N'-n-octylureidomethyl)-5–α-4-azaandrostan-3-one,

17ß-(N'-isopropylureidomethyl)-4-methyl-5α-4-azaandrostan-3-one,

17ß-((Iminodibenz-5-yl)carbonylaminomethyl)-4-methyl-5-α-4-azaandrostan-3-one,

17ß-(isobutyloxycarbonylaminomethyl)-4-methyl-5α-4azaandrostan-

3-one,
20-(Ethoxycarbonylamino)-4-methyl-5α-4-aza-pregnan-3-one,

4-Methyl-17ß-(N'-octadecylureidomethyl)-5α-4-aza-androstan-3-one,

17ß-(N'-(2-Ethylphenyl)ureidomethyl)-5α-4-azaandrostan-3-one,

20-(N'-(3-Chlorophenyl)ureido)-5α-4-azapregnan-an-3-one,

4-Methyl-20-(N'-phenylureido)-5α-4-azapregnan-3-one,

17ß-(N'-(2'3,-Dichlorophenyl)ureidomethyl)-4-methyl-5α-4 azaandrostan-3-one,

4-Methyl-17ß(N'-(naphth-2-yl)ureidomethyl)-5α-4-azaandrostan-3-one,

4-Methyl-17ß(N'-thiazol-2-ylureidomethyl)-5α-4-azaandrostan-3-one,

17β-(N'(Adamant-1-yl)thioureidomethyl)-4-methyl-5-α-4-azaandrostan-3-one,

17β-((1-Adamantyloxy)-carbonylaminomethyl)-5-α-4-methyl-4-azaandrostan-3-one,
or
4-Methyl-20-(N'-thien-2-ylmethylureido)-5α-4-azapregnan-3-one.

6. The compound according to Claim 4 and the pharmaceutically acceptable salts thereof, wherein the compound is selected from:

17ß-(N'-t-Butylureidomethyl)-4-methyl-5-α–4-azaandrost-1-en-3-one,

4-Methyl-17ß-(N'-phenylureidomethyl-5α-4-azaandrost1-en-3-one,

4-Methyl-20-(N'-methylureido)-5α-4-azapreg-1-en-3-one,

4-Methyl-17ß-(N'-n-propylureidomethyl-5-α–4-aza-androst-1-en-3-one,

4-Methyl-17ß-(N'-n-octylureidomethyl)-5-α–4-azaandrost-1-en-3-one,

17ß-(N'-isopropylureidomethyl)-4-methyl-5α-4-azaandrost-1-en-3-one,

17ß-((Iminodibenz-5-yl)carbonylaminomethyl)-4-methyl-5-α-4-azaandrost-1-en-3-one,

17ß-(isobutyloxycarbonylaminomethyl)-4-methyl-5α-4-azaandrost-1-en-3-one,

20-(Ethoxycarbonylamino)-4-methyl-5α-4-aza-preg-1-en-3-one,

4-Methyl-17ß-(N'-octadecylureidomethyl)-5α-4-azaan-drost-1-en-3-one,

17ß-(N'-(2-Ethylphenyl)ureidomethyl)-5α-4-azaandrost-1-en-3-one,

20-(N'-(3-Chlorophenyl)ureido)-5α-4-azapreg-1-en-3-one,

4-Methyl-20-(N'-phenylureido)-5α-4-azapreg-1-en-3-one,

17ß-(N'-(2'3,-Dichlorophenyl)ureidomethyl)-4-methyl-5α-4-azaandrost-1-en-3-one,

4-Methyl-17ß(N'-(naphth-2-yl)ureidomethyl)-5α-4-aza-androst-1-en-3-one,

4-Methyl-17ß(N'-thiazol-2-ylureidomethyl)-5α-4-aza-androst-1-en-3-one,

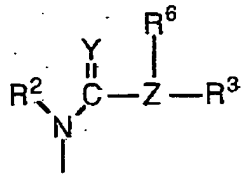
17β-(N'(Adamant-1-yl)thioureidomethyl)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17β-((1-Adamantyloxy)-carbonylaminomethyl)-5-α-4-methyl-4-azaandrostan-1-en-3-one, or

4-Methyl-20-(N'-thien-2-ylmethylureido)-5α-4-azapreg-1-en-3-one.

7. A compound according to Claim 1 and the pharmaceutically acceptable salts thereof, wherein:

A is



except when R^2 equals H, Y equals O and Z equals N and there is a 5αH, R^6 and R^3 cannot be independently selected from H, C_{1-8}alkyl, C_{3-6}cycloalkyl, phenyl or when R^6 and R^3 are taken together with the adjacent N to form a 5-6 membered ring comprising up to one other heteroatom selected from O or N;

wherein

R^1 is:

H, methyl or ehtyl;

R^2 is:

H, or
C_{1-12} alkyl;

R^3 is:

H,
C_{1-20} alkyl,
C_{6-14} arylC_{1-20}alkyl,
C_{3-20}cycloalkyl,
C_{3-20}cycloalkylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{1-20}alkylcarbonylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
carboxyC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
hydroxyC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxyC_{1-20}alkyl,
heteroaryl,
C_{6-14} aryl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
C_{6-14} arylcarbonylarylC_{1-20}alkyl,
halohydroxylC_{1-20}alkyl,
diarylC_{1-20}alkyl,
triarylC_{1-20}alkyl,
C_{2-20} alkenylC_{1-20}alkyl,
haloC_{1-20}alkyl,
C_{1-20} alkyloxyC_{1-20}alkyl,
C_{2-20}alkenylC_{1-20}alkyl,
C_{1-20} alkylthioC_{1-20}alkyl,
C_{1-20} alkylsulfonylC_{1-20}alkyl, or
C_{1-20} alkylsulfinylC_{1-20}alkyl;

R^6 is present when Z equals N and is:
H,
equivalent to R^3, or
C_{1-20} alkyl; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

Y is:

O, or
S;

Z is:

N, or
O.

8. A compound according to Claim 7 and the pharmaceutically acceptable salts thereof, wherein

R^1 is:

H, methyl or ethyl;

R^2 is:

H, or
C_{1-12} alkyl;

R^3 is:

-t-butyl,
3-thienyl,
-2-thienyl,
-11-(isopropylthio)undecyl,
-7-(carbomethoxy)heptyl,
-(4-isobutylbenzene)ethyl,
-7-(carboxy)heptyl,
-acetylmethyl,
-1-adamantylmethyl,
-2-thienylmethyl,
-2-(carbobenzyloxy)ethyl,
-(3,4 dimethoxyphenyl)methyl,
-phenyl,
-5-bromopentyl,
-11-hydroxyundecyl,
-1(4-nitrophenyl)ethyl,

-isopropylthiomethyl,
-benzyloxymethyl,
-carbomethoxymethyl,
-diphenylmethyl,
-triphenylmethyl,
-2-furyl,
4-isopropylphenyl,
cyclohexylmethyl,
4-methylcyclohexyl,
3-(3-Indolyl)propyl,
3-Indolylmethyl,
4-isobutylbenzyl,
4-nitrophenylbenzyl,
3-acetamidomethyl,
4-ethoxybenzyl,
hexadecyl,
stearyl,
3,5 Bis(trifluoromethyl),
3-cyanobenzyl,
heptaflouropropyl,
4-benzoylbenzyl,
5-benztriazolyl,
3,5 difluorobenzyl,
Bis(4-isopropylphenyl)methyl,
2-hydroxybenzyl,
methyl,
allyl,
n-propyl,
n-octyl,
isopropyl,
isobutyl,
ethyl,
benzyl,
octadecyl,

2(ethyl)phenyl,
3(chloro)phenyl,
4(methyl)phenyl,
2,3(dichloro)phenyl,
4(fluoro)phenyl,
3(methoxy)phenyl,
2(ethoxy)phenyl,
2(napthyl) or,
2-thiazolnyl;

R^6 is present when Z equals N and is:

H,
equivalent to R^3, or
C_{1-20} alkyl; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

Y is:

O, or
S;

Z is:

N, or
O.

9. The compound according to Claim 8 and the pharmaceutically acceptable salts thereof, wherein the compound is selected from:

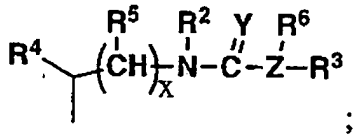
17-(N'-Allylureido)-4-methyl-5α-4-azaandrostan-3-one,
4-Methyl-17β-(N'-(4-(trifluromethoxy)phenyl))-5-α-4-azaandrostan-3-one,
17-(N'-(4-fluorophenyl)ureido)-5-α–4-azaandrostan-3-one, or
17-(N'-(3-Methoxyphenylureido)-5α-4-azaandrostan-3-one.

10. The compound according to Claim 8 and the pharmaceutically acceptable salts thereof, wherein the compound is selected from:

17-(N'-Allylureido)-4-methyl-5α-4-azaandrost-1-en-3-one,
4-Methyl-17β-(N'-(4-(trifluromethoxy)phenyl))-5-α-4-azaandrostan-1-in-3-one,
17-(N'-(4-fluorophenyl)ureido)-5α-4-azaandrost-1-en-3-one, or
17-(N'-(3-Methoxyphenyl)ureido)-5α-4-azaandrost-1-en-3-one.

11. A compound according to Claim 1 and the pharmaceutically acceptable salts thereof, wherein:

A is:



; wherein

R^1 is:

H, methyl or ethyl;

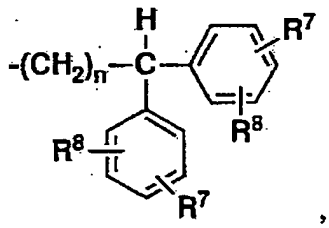
R^2 is:

H, or
C_{1-20} alkyl;

R^3 is:

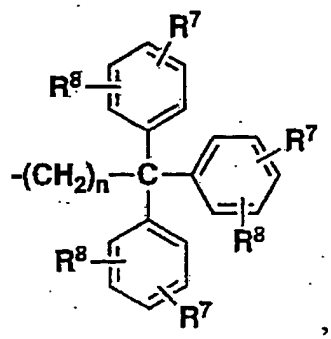
H,
C_{1-20} alkyl,
C_{6-14} arylC_{1-20}alkyl,

C_{3-20}cycloalkyl,
C_{3-20}cycloalkylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{1-20}alkylcarbonylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
carboxylC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
hydroxylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxyC_{1-20}alkyl,
heteroaryl,
C_{6-14} aryl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
C_{2-20} alkenylC_{1-20}alkyl,
C_{1-20}alkyloxyC_{1-20}alkyl,
C_{6-14} arylcarbonylC_{6-14}arylC_{1-20}alkyl,
halohydroxylC_{1-20}alkyl,
diarylC_{1-20}alkyl of the formula:



, n equals 0-19;

triarylC_{1-20}alkyl of the formula:



, n equals 1-19;

halo C_{1-20}alkyl,

C_{1-20}alkylxoyC_{1-20}alkyl,
C_{1-20}alkylthioC_{1-20}alkyl,
C_{1-20}alkylsulfonylC_{1-20}alkyl, or
C_{1-20}alkylsulfinylC_{1-20}alkyl;

R^4 is:
H,
C_{1-20} alkyl,
heteroaryl, or

C_6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen;

R^6 is present when Z equals N and is independently
H,
C_{1-20} alkyl, or
equivalent to R^3; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

R^7 or R^8 are:

H,
CH_3,
C_2H_5,
carboxamido,
OH,

OCH_3,
NO_2,
CN,
F,
RS,
RSO,
RSO_2,
R_2N, where R can be the same or different selected from H, C_1-C_4 alkyl, or C_6-C_{10} aryl;
Cl,
acetamido,
OC_2H_5,
CF_3,
isopropyl, or
isobutyl; n equals 1-10 and the C_{1-20}alkyl portion is optionally substituted with R^5;

Y is:

O, or
S;

Z is:

N, or
O; and

x is an integer from 1-10.

12. A compound according to Claim 11 and the pharmaceutically acceptable salts thereof, wherein

R^1 is:

H, or methyl or ethyl;

R^2 is:

H, or
C_{1-12} alkyl;

R^3 is:

-t-butyl,
3-thienyl,
-2-thienyl,
-11-(isopropylthio)undecyl,
-7-(carbomethoxy)heptyl,
-(4-isobutylbenzene)ethyl,
-7-(carboxy)heptyl,
-acetylmethyl,
-1-adamantylmethyl,
-2-thienylmethyl,
-2-(carbobenzyloxy)ethyl,
-3,4 dimethoxyphenylmethyl,
-phenyl,
-5-bromopentyl,
-11-hydroxyundecyl,
-1(4-nitrophenyl)ethyl,
-isopropylthiomethyl,
-benzyloxymethyl,
carbomethoxymethyl,
-diphenylmethyl,
-triphenylmethyl,
-2-furyl,
4-isopropylphenyl,
cyclohexylmethyl,
4-methylcyclohexyl,
3-(3-Indolyl)propyl,

3-Indoylmethyl,
4-isobutylbenzyl,
4-nitrobenzyl,
3-acetamidomethyl,
4-ethoxybenzyl,
hexadecyl,
stearyl,
3,5 Bis(triflouromethyl),
3-cyanobenzyl,
heptaflouropropyl,
4-benoylbenzyl,
5-benztriaoolyl,
3,5 diflourobenzyl,
Bis (4-isopropylphenyl)methyl,
2 hydroxybenzyl,
methyl,
allyl,
n-propyl,
n-octyl,
isopropyl,
isobutyl,
ethyl,
benzyl,
octadecyl,
2(ethyl)phenyl,
3(chloro)phenyl,
4(methyl)phenyl,
2,3(dichloro)phenyl,
4(flouro)phenyl,
3(methoxy)phenyl,
2(ethoxy)phenyl,
2(napthyl), or
2-thiazoyl;

R^4 is:

H,
C_{1-13} alkyl,
heteroaryl, or
C_6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen;

R^5 can be the same or different when x is greater than 1 and is:
H, or
C_{1-12} alkyl,
heteroaryl, or
C_{6-14} aryl;

R^6 is present when Z equals N and is independently
H,
C_{1-20} alkyl, or
equivalent to R^3; or taken together with R^3 and the N to which they are attached represent a heteroaryl ring system;

Y is:

O, or
S;

Z is:

N, or
O;

x is an integer from 1-10.

13. The compound according to Claim 12, wherein the compound is selected from:

20-(N'-t-butylureidomethyl)-4-methyl-5α-4-azapregnan-3-one,
20-((Iminodibenz-5-yl)carbonylaminomethyl)-4-methyl-5α-4-azapregnan-3-one,
20-(Benzyloxycarbonylaminomethyl)-5α-4-azapregnan-3-one,
20-(N'-p-tolylureidomethyl)-5α-4-azapregnan-3-one, or
20-(N'-(2-Ethoxyphenyl)ureidomethyl)-4-methyl-5α-4-azapregnan-3-one.

14. The compound according to Claim 12, wherein the compound is selected from:

20-(N'-t-butylureidomethyl)-4-methyl-5α-4-azapreg-1-en-3-one,
20-((Iminodibenz-5-yl)carbonylaminomethyl)-4-methyl-5α-4-azapreg-1-en-3-one,
20-(Benzyloxycarbonylaminomethyl)-5α-4-azapreg-1-en-3-one,
20-(N'-p-tolylureidomethyl)-5α-4-aza-preg-1-en-3-one, or
20-(N'-(2-Ethoxyphenyl)ureidomethyl)-4-methyl-5α-4-azapreg-1-en-3-one.

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

16. A method of treating benign prostatic hyperplasia, acne, female hirsutism, male pattern baldness, androgenic alopecia, prostatitis, and/or preventing prostatic carcinoma in a human host in

need of such treatment comprising the step of administering to said host a therapeutically effective amount of the compound defined in Claim 1.

17. The method of Claim 16 wherein said compound is an inhibitor of 5α-reductase 1.

18. The method of Claim 16 wherein said compound is an inhibitor of 5α-reductase 2.

19. The method of Claim 16 wherein said compound is a dual inhibitor of both 5α-reductase 1 and 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04634

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K31/45 CO7D 221/02

US CL :~~A61K 31/470~~ 546/77; 514/284

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : A61K 31/470; 546/77; 514/284

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS online structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Jour. Clinical Endoc and METAB., Vol 74 1992, Diani et al. "Hair Growth effects of oran administration of fina steride, a steroids reductase inhibitor, alone and in combination on with topical minoxidil in the balding stumptail macaque pages 345-350. See page 345, para. bridging cols 1-2, last 3 lines.	16-19
A	J. ORG. CHEM Vol 46, 1981 back oxidation of azasteroid lactams and alcohols with benzeneslenic anhydride" pages 1442-6.	[illegible]
A	Jour, Med. CHEM, Vol 27, 1984 Rasmusson et al. "Azasteroids as inhibitors of Rat prostatic 52 Reductase" pages 1690-1701.	1-19

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

13 JULY 1993

Date of mailing of the international search report

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Box PCT
Washington, D.C. 20231

Facsimile No. NOT APPLICABLE

Authorized officer

Caitlyn Elmore for
D.G. DAVIS

Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04634

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Jour. Med. CHEM, Vol 29, 1986, Rasmusson et al. "A2A steroids: structure- activity relationship for inhibition of 52 Reductase and of androgen receptor binding pages 2298-2315.	1-19
A	E,P, B 0200859 (Cainelli et al) 12 November 1986. See entire document.	1-19
X	U.S, A, 4377584 (Rasmussion et al) 22 March 1983. See claimed 14, 16-18.	1,2,7-10, 15-19
A	U.S., 4760071 (Ramusson et al) 26 July 18 1988. See entire document.	1-19
A	U.S., 5049562 (Ramusson et al.) 17 September 1991. see entire document.	1-19
X, P	U.S. 5116983 (Bhahacharya et al.) 26 May 1992, See Claim 1.	1,2,7-10, 15-19
A	U.S.A, 5110939 (Holt) 5 May 1992 see entire document.	1-19
A	Jour, Organic Chem. Vol 54, 1989 Back et al. "Nchloro azasteroids a novel class of reactive steroid analogues. Preparation, reaction with thiols and photochemical conversion to electrophilic N acyl Imines" pages 1904-10.	1-19
A	US, a. 4859, 681 (Rasmusson et al.) 8 August 1989. See entire document.	1-19